APPENDIX E

1998 Federal Research Conference

The Research Working Group Persian Gulf
Veterans Coordinating Board

CONFERENCE ON FEDERALLY SPONSORED GULF WAR VETERANS' ILLNESSES RESEARCH

The Doubletree Hotel
Pentagon City - National Airport
June 17-19, 1998

Proceedings

PREFACE

It is my pleasure to provide you with this report of the Conference on Federally Sponsored Gulf War Veterans' Illnesses Research that was held June 17-19, 1998 in Arlington, Virginia. This is the third conference of its type, the first one being held at the Armed Forces Institute of Pathology in 1995 and the second one at Fort Detrick, Maryland in 1997. From 1995 to the present the conference has grown from about 50 participants to now nearly 300. This growth reflects the vigor of the research activities carried out by federal and federally sponsored researchers on behalf of veterans of the Gulf War.

In 1990 and 1991 the United States of America deployed nearly 700,000 troops to Saudi Arabia and surrounding areas in response the invasion of Kuwait by Iraqi forces. Although the ensuing Gulf War is noted for its swift completion with minimal casualties to U.S. forces in the theater of operations, the U.S. government did not anticipate the emergence of unexplained and undiagnosed illnesses among the veterans of the Gulf War upon their return home.

By 1994, the government had embarked on a mission to conduct extensive research on the nature and potential cause(s) of these illnesses. From 1994 to the present the federal government has conducted or sponsored over 121 research projects with a financial commitment of over $115 million. .

The purpose of the Conference was to bring federally sponsored researchers on Gulf War veterans' illnesses together in a common forum to:

- Communicate and exchange new results from ongoing research programs
- Engender new ideas on Gulf War veterans' illnesses
- Establish connections/collaborations with other researchers
- Hear from experts about the broad methodological issues and problems in Gulf War veterans illnesses research
- Learn how different aspects of Gulf War illnesses research (clinical, epidemiology, basic) should fit together to form a comprehensive view of these illnesses that can inform policy makers
- Provide research and policy leaders in federal agencies with up-to-date progress reports on emerging research findings
- Allow clinicians to hear firsthand some of the latest research findings

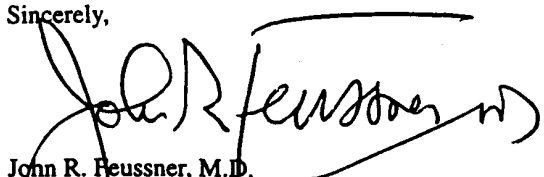
Over the course of two and one-half days, the meeting was organized around three morning plenary sessions, two afternoon breakout sessions on specific research topics, and one evening poster session.

The plenary sessions were intended to be of broad appeal to the wider audience of participants. Nationally and internationally recognized experts spoke on their fields of expertise as they relate to issues surrounding Gulf War veterans' illnesses. The breakout sessions and the poster session provided researchers forums to present their research findings in a wide array of scientific areas, including nosology, epidemiology, toxicology, psychological, neuropsychological, determination of exposure and exposure/response relationships, reproductive health, and the neurobiological correlates of stress.

The proceedings of the Conference presented here contain the texts of the material provided by each plenary speaker and summaries of each breakout session. These summaries were prepared by the co-chairs of each session, and consequently could vary in style. There is a complete set of submitted abstracts from speakers in the breakout sessions and poster session.

It is through continuous rigorous scientific research that we will begin to better understand the nature and potentially the causes of Gulf War veterans' illnesses. It is, however, of potentially even greater importance that we use this research to improve the health of Gulf War veterans. This Conference is just one aspect of the research process that will lead us to these goals.

Sincerely,



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MEETING AGENDA — WEDNESDAY, JUNE 17, 1998

Wednesday, June 17, 1998

8:00 AM	**REGISTRATION** Continental Breakfast Available
9:00 AM - 12:45 PM	**PLENARY SESSION** Timothy R. Gerrity, Chair
9:00 AM	**Introduction/Welcome** **Overview of the Federal Research Program** Timothy R. Gerrity
9:30 AM	**Keynote** **Methodological Challenges in Epidemiologic Research on the Health of Gulf War Veterans** David A. Savitz
10:00 AM	**Nosologic Challenges of Diagnostic Criteria for a "New Illness"** Alvan R. Feinstein
10:30 AM	BREAK
10:45 AM	**Overlapping Syndromes** Dedra Buchwald
11:15 AM	**Symptoms in Gulf War Veterans and the General Population** Kurt Kroenke

11:45 AM	**Factor Analysis and Related Methods in Epidemiological Research** Stanley A. Mulaik
12:15 PM	**Panel Discussion**
12:45 PM -2:00 PM	LUNCH BREAK
2:00 PM -5:00 PM	**CONCURRENT BREAKOUT SESSIONS**
2:00 PM - 5:00 PM	**Session A: Defining Illnesses I** ◊ Alvan R. Feinstein, Co-Chair ◊ Simon Wessely, Co-Chair IDENTIFYING NEW CAUSES OF DISEASE: HISTORICAL EXAMPLES AND THE DILEMMA OF ILLNESSES IN GULF WAR VETERANS ◊ Gary D. Gackstetter DEFINING ILL-HEALTH IN THREE BRITISH MILITARY COHORTS ◊ Khalida Ismail GULF WAR DISEASES: A CRITICAL REVIEW OF 400 EXAMINATIONS ◊ Foster Marshall ILL-DEFINED CONDITIONS IN GULF WAR VETERANS: FINDINGS FROM THE COMPREHENSIVE CLINICAL EVALUATION PROGRAM ◊ Michael J. Roy MUSCULOSKELETAL SYNDROMES OF DEPLOYED PERSIAN GULF WAR VETERANS ◊ Andre Barkhuizen
2:00 PM - 5:00 PM	**Session B: Epidemiology** ◊ David M. Ozonoff, Co-Chair ◊ Gregory C. Gray, Co-Chair NATIONAL HEALTH SURVEY OF GULF WAR ERA VETERANS AND THEIR FAMILIES ◊ Han K. Kang VALIDATION OF SELECTED VETERAN-REPORTED HEALTH OUTCOMES IN THE NATIONAL HEALTH SURVEY OF GULF WAR ERA VETERANS ◊ Carol A. Magee (1) IS THE GULF WAR SYNDROME DUE TO STRESS? THE EVIDENCE FROM FEDERALLY SPONSORED STUDIES REEXAMINED, (2) EVIDENCE FOR EXCESS RATES OF BIRTH DEFECTS IN GULF WAR VETERANS FROM REANALYSIS OF FINDINGS FROM FEDERALLY SPONSORED STUDIES, (3) SELECTION BIAS FROM THE "HEALTHY-WARRIOR EFFECT" AND UNEQUAL FOLLOWUP IN FEDERALLY SPONSORED SURVEYS OF GULF WAR VETERANS ◊ Robert W. Haley ILLNESS AND HEALTH CARE SEEKING IN PERSIAN GULF VETERANS PRIOR TO DEPLOYMENT ◊ Richard N. Miller and Eric T. Lund THE HEALTH OF POTENTIAL NON-PARTICIPANTS IN A UK PILOT STUDY OF VETERANS ◊ Gary J. Macfarlane and Nicola M. Cherry

2:00 PM - 5:00 PM **Session C: Toxicology**
◊ Barry R. Wilson, Co-Chair ◊ Peter S. Spencer, Co-Chair

FAILURE OF PYRIDOSTIGMINE PRETREATMENT TO PROTECT AGAINST THE EFFECTS OF CHLORPYRIFOS
◊ David H. Overstreet

FINGER STICK BASED ASSAYS OF BLOOD CHOLINESTERASE LEVELS
◊ Barry W. Wilson

THE EFFECTS OF PYRIDOSTIGMINE BROMIDE, PERMETHRIN AND DEET ALONE, OR IN COMBINATION, ON FIXED-RATIO AND FIXED-INTERVAL BEHAVIOR IN MALE SPRAGUE-DAWLEY RATS
◊ Frans van Haaren

MASKED ASSAY FOR GENOMIC INSTABILITY IN A GULF WAR ILLNESS GROUP VS 3 MATCHED CONTROL GROUPS
◊ William N. Fishbein

THE IMMUNOMODULATORY EFFECTS OF THE CHEMICALS USED DURING THE GULF WAR
◊ Janet L. Karlix

2:00 PM - 5:00 PM **Session D: Psychological and Neuropsychologial Outcomes**
◊ Jessica Wolfe, Chair

ESTIMATING PRE-WAR COGNITIVE FUNCTIONING IN GULF WAR VETERANS
◊ Raymond K. Dipino

NEUROPSYCHOLOGICAL FINDINGS AMONG PERSIAN GULF WAR VETERANS
◊ Roberta F. White

STRESS, PERSONALITY, & COPING IN GULF WAR VETERANS WITH FATIGUING ILLNESS
◊ Nancy Fiedler

CONCURRENT AND LONGITUDINAL PREDICTION OF PHYSICAL SYMPTOMS IN GULF WAR VETERANS
◊ Patrick Sloan

FUNCTIONAL STATUS AND MOOD IN GULF WAR VETERANS (GWVs) WITH FATIGUING ILLNESS
◊ Lana A. Tiersky

5:00 PM - 7:00 PM **POSTER SESSION AND RECEPTION**

Thursday, June 18, 1998

7:45 AM - 8:30 AM **Clinician Sunrise Session**
Susan Mather, Chair

8:00 AM **REGISTRATION**
Continental Breakfast Available

8:30 AM - 12:30 PM **PLENARY SESSION**
John Graham, Chair

8:35 AM	**Exposure and Exposure-Response Relationships** David M. Ozonoff
9:05 AM	**Complex and Multi-exposure Responses** Raymond S. H. Yang
9:35 AM	**Measuring Reproductive Outcome** Patricia Doyle
10:05 AM	**Panel Discussion**
10:35 -10:45 AM	BREAK
10:45 AM	**The Biology of Stress** Leslie J. Crofford
11:15 AM	**Communicating Health Information, Lessons-Learned** Max Lum
	Risk Communication Case Study: Communicating Exposure Assessment and Clinical Outcome Results to Veterans Exposed to Depleted Uranium During the Gulf War ◊ Kathleen M. McPhaul
11:45 AM	**Panel Discussion**
12:30 PM - 2:00 PM	LUNCH BREAK
2:00 PM - 4:30 PM	**Clinician Meeting** Frances Murphy, Chair
2:00 PM - 5:00 PM	**CONCURRENT BREAKOUT SESSIONS**
2:00 PM - 5:00 PM	**Session E: Defining Illnesses II** ◊ Timothy R. Gerrity, Co-Chair ◊ Linda A. McCauley, Co-Chair
	FACTOR ANALYSIS OF SELF-REPORTED SYMPTOMS. DOES IT IDENTIFY A GULF WAR SYNDROME? ◊ James D. Knoke
	PERSIAN GULF WAR (PGW) UNEXPLAINED ILLNESS (UI): CASE DEFINITION ◊ Michael L. Wynn
	PERSISTENCE AND UNEXPLAINED NATURE OF HEALTH SYMPTOMS AMONG PERSIAN GULF WAR VETERANS ◊ Linda A. McCauley
	MEDICAL EVALUATION OF PERSIAN GULF VETERANS WITH FATIGUE AND/OR CHEMICAL SENSITIVITY ◊ Claudia A. Pollet
	PERCEIVED EXPOSURE TO CHEMICAL WEAPONS AND UNEXPLAINED ILLNESS AMONG MILITARY AND CIVILIAN SUBJECTS ◊ Peter S. Spencer
2:00 PM - 5:00 PM	**Session F: Exposure and Exposure/Response Relationships** ◊ David M. Ozonoff, Co-Chair ◊ Raymond S. H. Yang, Co-Chair

USE OF THE TROOP LOCATION DATABASE AND GEOGRAPHIC INFORMATION SYSTEM (GIS) TECHNOLOGY FOR ESTIMATING ENVIRONMENTAL EXPOSURES AND CONDUCTING EPIDEMIOLOGICAL RESEARCH
◊ Jack M. Heller

HOSPITALIZATION RISK AFTER POSSIBLE EXPOSURE TO IRAQI CHEMICAL MUNITIONS DESTRUCTION DURING THE PERSIAN GULF WAR
◊ Gregory G. Gray

ASTHMA AND EXPOSURE TO OIL FIRE SMOKE AMONG GULF WAR VETERANS
◊ Jeff L. Lange

A METHOD FOR COMPARING SELF-REPORTED DEPLETED URANIUM EXPOSURE IN A COHORT OF PERSIAN GULF VETERANS
◊ Frank J. Hooper

SUMMARY OF ENVIRONMENTAL INTERVIEW DATA FROM PERSIAN GULF WAR (PGW) VETERANS
◊ Susan P. Proctor

2:00 PM - 5:00 PM **Session G: Reproductive Outcomes**
◊ Patricia Doyle, Co-Chair ◊ Maria Rosario G. Araneta, Co-Chair

NAVAL BIRTH DEFECTS REGISTRY FEASIBILITY STUDY
◊ Ruth A. Bush

THE NATIONAL STUDY ON REPRODUCTIVE OUTCOMES: INITIAL FINDINGS
◊ Paul A. Sato and Katia M. Hiliopoulos

REPRODUCTIVE AND PERINATAL OUTCOMES AMONG CONCEPTIONS AND PREGNANCIES DURING THE PERSIAN GULF WAR
◊ Maria Rosario G. Araneta

ENDOGENOUS PREDICTORS IN MULTIPLE REGRESSION: BIRTHWEIGHT AND GESTATIONAL AGE AMONG GULF WAR-EXPOSED PREGNANCIES
◊ Victor M. Gastanaga

2:00 PM - 5:00 PM **Session H: Neurobiology of Stress**
◊ Daniel J. Clauw, Co-Chair ◊ Leslie Crofford, Co-Chair

PHYSIOLOGIC ABNORMALITIES IN FIBROMYALGIA, CHRONIC FATIGUE SYNDROME, AND GULF WAR ILLNESS
◊ Daniel J. Clauw

NEUROENDOCRINE TESTING OF DEPLOYED PERSIAN GULF WAR VETERANS WITH UNEXPLAINED MUSCULOSKELETAL SYMPTOMS
◊ Andre Barkhuizen

SERIAL CORTICOTROPIN-RELEASING HORMONE LEVELS AND ADRENOCORTICAL ACTIVITY IN COMBAT VETERANS WITH POSTTRAUMATIC STRESS DISORDER
◊ Dewleen G. Baker

CAN PTSD CAUSE PHYSICAL SYMPTOMS? A HYPOTHESIS SCREEN USING REGISTRY DATA
◊ Charles C. Engel, Jr.

ALTERED IMMUNE STATUS IN GULF VETERANS BUT NOT CIVILIANS WITH CHRONIC FATIGUE SYNDROME
◊ Benjamin H. Natelson

PTSD AND IMMUNE DYSREGULATION IN GULF WAR VETÉRANS
◊ Michael P. Everson

2:00 PM - 5:00 PM **Session I: Other Health Outcomes**
◊ John T. Graham, Co-Chair ◊ Dennis N. Bourdette, Co-Chair

EVALUATION OF PERSIAN GULF WAR VETERANS AND THEIR SEXUAL PARTNERS WITH BURNING SEMEN SYNDROME
◊ Jonathan A. Bernstein

ANTILEISHMANIAL DRUG DEVELOPMENT: EXPLOITATION OF PARASITE HEME DEPENDENCY
◊ Michael K. Riscoe

IMMUNE RESPONSE TO A *LEISHMANIA TROPICA* RECOMBINANT PROTEIN AMONG PERSIAN GULF WAR (PGW) VETERANS: RESULTS FROM A CASE-CONTROL STUDY
◊ Dennis N. Bourdette

GALLBLADDER DISEASE IN GULF WAR VETERANS
◊ Boaz I. Milner

5:00 PM - 7:00 PM **POSTER SESSION**

Friday, June 19, 1998

7:45 AM - 8:45 AM **Clinician Sunrise Session**
Frances Murphy, Chair

8:00 AM **REGISTRATION**
Continental Breakfast Available

9:00 AM **PLENARY SESSION**
Michael E. Kilpatrick, Chair

9:05 AM **Treating Difficult to Diagnose and Ill-Defined Conditions: Translating New Advances in Our Understanding of Mechanisms into More Effective Treatments**
Daniel J. Clauw

9:35 AM **Force Health Protection**
Richard M. Cocrane

10:05 AM **Improving the Health of Our Military, Veterans and Their Families: A Strategic Plan for Research**
Timothy R. Gerrity

10:35 AM **Panel Discussion**

11:05 AM **Health Status of Gulf War Troops: Lessons Learned**
Robert H. Roswell

Plenary Session Abstracts

Overview of the Federal Research Program

Timothy R. Gerrity, Ph.D.
Office of Research and Development
U.S. Department of Veterans Affairs

Introduction

The United States deployed approximately 697,000 military personnel to the Persian Gulf area to serve in Operations Desert Shield and Desert Storm. During these Operations, military personnel were subject to a variety of exposures, both natural and man-made, that could have harmful health effects. Within a year of their return from the Persian Gulf area, a number of Gulf War veterans began to experience a broad range of health-related symptoms. They have also expressed concern about possible Gulf War relationships to spousal illnesses, poor pregnancy outcomes, and birth defects in children conceived after the war.

Because of these concerns, the Federal Government undertook the development of a comprehensive and coordinated research program. On August 31, 1993, in response to Public Law 102-585, President William J. Clinton named the Secretary of Veterans Affairs (VA) to coordinate research funded by the Executive Branch of the Federal Government into the health consequences of service in the Gulf War. VA carries out its research-coordinating role through the auspices of the Research Working Group (RWG) of the Persian Gulf Veterans Coordinating Board (PGVCB). The Secretaries of the Departments of Defense (DoD), Health and Human Services (HHS), and VA chair the PGVCB and have representatives on the RWG. Because of the potential link between environmental factors and Gulf War veterans' illnesses, the U.S. Environmental Protection Agency (EPA) is also a member of the RWG.

The VA Office of Research and Development has the primary responsibility for coordinating the federal research effort toward clarifying health problems related to service in the Gulf War.

The principal charge to the RWG is to:

- Assess the state and direction of ongoing research;
- Identify gaps in knowledge;
- Identify testable hypotheses;
- Recommend research directions;
- Review developing concepts;
- Collect and disseminate information;
- Ensure that the right research is done; and
- Ensure appropriate review and oversight of research.

Membership on the RWG consists of senior research scientists and clinical managers from VA, DoD, HHS, and EPA. Figure 1 shows the structure of the RWG with its subcommittees.

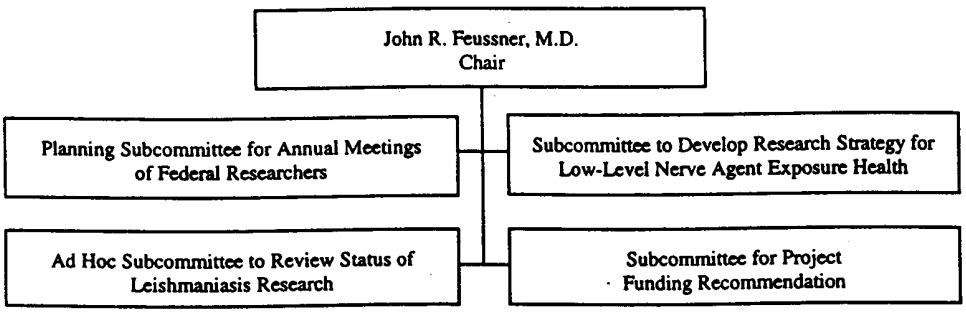

Figure 1. Research Working Group Organization

Since its inception, the RWG has accomplished a number of important tasks in the process of organizing and coordinating the federal research effort. These include:

- Four comprehensive annual reports to Congress on Gulf War veterans' illnesses research[1-4]
- A strategic plan for research (*A Working Plan for Research on Persian Gulf Veterans Illnesses*[5])
- A strategic plan for research on the health effects of exposure to low levels of organophosphorous nerve agents[4]
- Programmatic review of peer-reviewed, competed research proposals leading to funding recommendations for over $100 million in research projects
- Three national and international meetings of federally funded researchers
- Sponsorship of a workshop in conjunction with the Society of Toxicology on the potential health consequences of low-level exposure to chemical warfare nerve agents
- Follow-up investigation of preliminary reports of positive experimental serological tests for leishmaniasis[4]

Setting the Research Agenda

In 1995 the RWG recognized the need for a systematic approach to the management of the federal research portfolio and developed a strategic plan for the conduct of research on Gulf War veterans' illnesses (for conciseness it will be referred to as the *Working Plan*)[5]. To reflect and account for newly acquired information and knowledge, the *Working Plan* has undergone one major revision (November 1996), and it is currently undergoing another.

The *Working Plan* has three stated goals for research on Gulf War veterans' illnesses:

- Determine the nature and prevalence of symptoms, diseases, and other conditions among Gulf War veterans;
- Identify risk factors for symptoms, diseases, and other conditions; and
- Identify diagnostic tools, treatment methods, and prevention/intervention strategies.

Both the first and the revised *Working Plans* contain about 20 research questions in the broad areas of exposure and health outcome posed by Gulf War veterans' illnesses. In the context of these questions, the *Working Plan* has provided assessments of the state of ongoing research, and has identified specific research needs.

The original 1995 *Working Plan* articulated five research recommendations that should serve as the basis for new research at that time:

- Determine illness and symptom prevalence in Gulf War veterans;
- Determine illness and symptom prevalence in coalition forces and indigenous populations;
- Determine the prevalence of adverse reproductive outcomes; and
- Determine the long-term, cause-specific mortality of Gulf War veterans.

As reported in the Annual Reports to Congress for 1996 and 1997[3,4], significant progress has been made in initiating research in these areas. Answers to questions have begun to emerge. The only area for which there is no research is in the determination of illness and symptom prevalence in indigenous populations such as Saudi Arabia and Kuwait. The RWG has concluded that the ability to conduct sound reliable epidemiological studies in the area of the Gulf is severely limited for methodological reasons. However, the RWG remains alert to any new conditions that could modify that position.

In the 1996 revised *Working Plan*, new factual and conceptual knowledge about exposures and outcomes during and after the Gulf War led to a revised set of research recommendations that were divided into short-term and long-term recommendations. The long-term recommendations recognized the need to conduct research that may be less likely to directly answer questions about the cause and nature of Gulf War veterans' illnesses but are vitally important for planning future military deployments.

Short-Term Research Recommendations

- Epidemiological follow-up on Gulf War veterans' mortality experience at appropriate time intervals;
- Longitudinal follow-up studies of Gulf War veterans' health status; and
- Peer review of atmospheric exposure models for pollutants, such as the oil well fires, and chemical warfare agent releases at Khamisiyah, Iraq.

Long-Term Research Recommendations

- Research on risk factors for stress-related disorders;
- Research on risk factors for excess mortality due to accidents;
- Development of exposure biomarkers for chemical warfare agents;
- Toxicological and epidemiological research on the health effects of exposure to low concentrations of chemical warfare agents;
- Development of a strategic research plan for investigating the long-term health effects of low-level chemical warfare agent exposures; and
- Development of a simple, sensitive test for *L. tropica* infection.

These recommendations have been guiding the selection of new research projects since November 1996. The next section is an overview of the current research portfolio on Gulf War veterans' illnesses research that has been driven by the actions of the RWG through its various activities, including the development of the *Working Plan*.

The Research Portfolio

Since 1994 the Federal Government has sponsored 121 research projects (with new projects about to begin) and has committed $115 million in resources to these projects. Over half of these projects involve scientists outside of the government. Through February 1998, 39 of the 121 projects have been completed, 78 projects are ongoing, and 4 have been awarded funds that are pending startup.

Figure 2 shows the trend since 1994 of the number of active research projects taking different research approaches (basic, clinical, epidemiological, and applied, such as vaccine and drug development) toward understanding the health problems of Gulf War veterans.

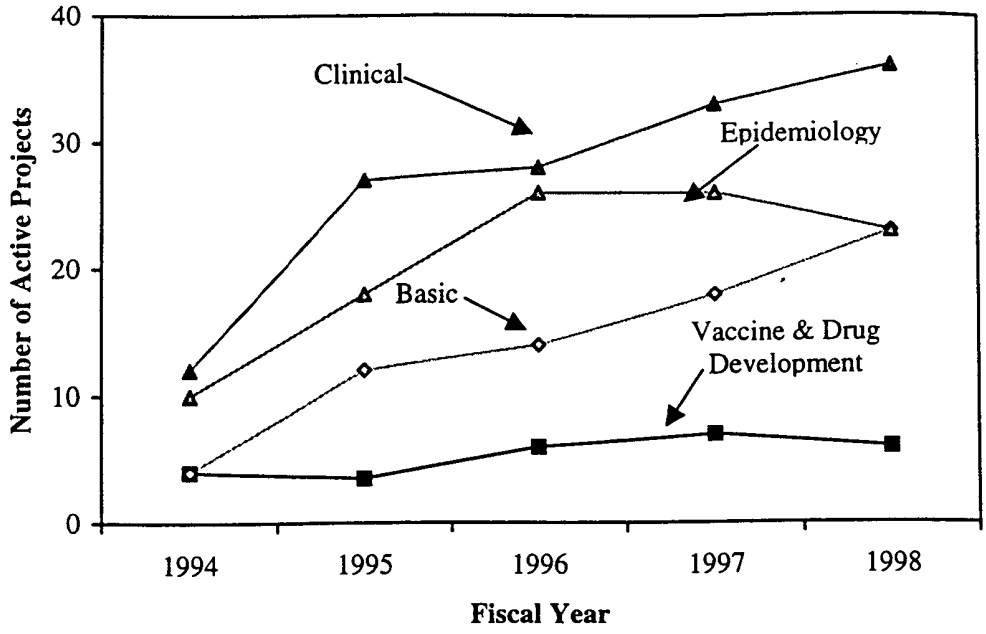

Figure 2. Number of Active Research Projects of Different Types for Each Fiscal Year

As the number of active research projects has increased from 32 in 1994 to as many as 90 in 1998, the patterns of investment have changed. The proportion of research projects funded in epidemiology research has appropriately declined, while the number of research projects concerned with the toxicology of chemical weapons, both in relative and absolute terms, has markedly increased.

Beginning in 1998 new research will begin to focus on treatments for Gulf War veterans. VA and DoD are investing over $10 million in two important clinical trials. The first will be a large multicenter study of the effectiveness of cognitive behavioral therapy (CBT) and exercise in ameliorating the nonspecific, multisymptomatic problems of Gulf War veterans that have been such a burden to them. The second treatment study will also be a large multicenter trial of the effectiveness of the antibiotic doxycycline in reducing symptomatic complaints in veterans. The decision to undertake the latter trial rests in part on the concern that a large number of veterans may be receiving this drug as a treatment of their symptoms without actual knowledge of its efficacy in the absence of positive proof of infection. Additionally, small single-site trials in the civilian community of antibiotics have demonstrated the possibility of symptomatic improvement in such conditions as rheumatoid arthritis.

Figure 3 shows the cumulative investment in research across various areas of research focus[a]. The nature of each research project in the portfolio is described by up to three focus areas, as appropriate. Investments are shown according to the primary focus area of each project, and according to all focus areas assigned to each project. The investment of funds has been greatest in the focus areas of the Brain and Nervous System and in Symptoms and General Health. The third largest investment is in the focus area of Diagnosis; that is, research directed toward characterizing Gulf War veterans' illnesses, and on specific diagnostic tests such as the research on a serological assay for leishmaniasis.

[a] Brain and Nervous System; Chemical Weapons; Depleted Uranium; Diagnosis; Environmental Toxicology; Immunology; Interactions; Leishmaniasis; Mortality; Prevention; Pyridostigmine Bromide, Reproductive Health; Symptoms and General Health; Treatment

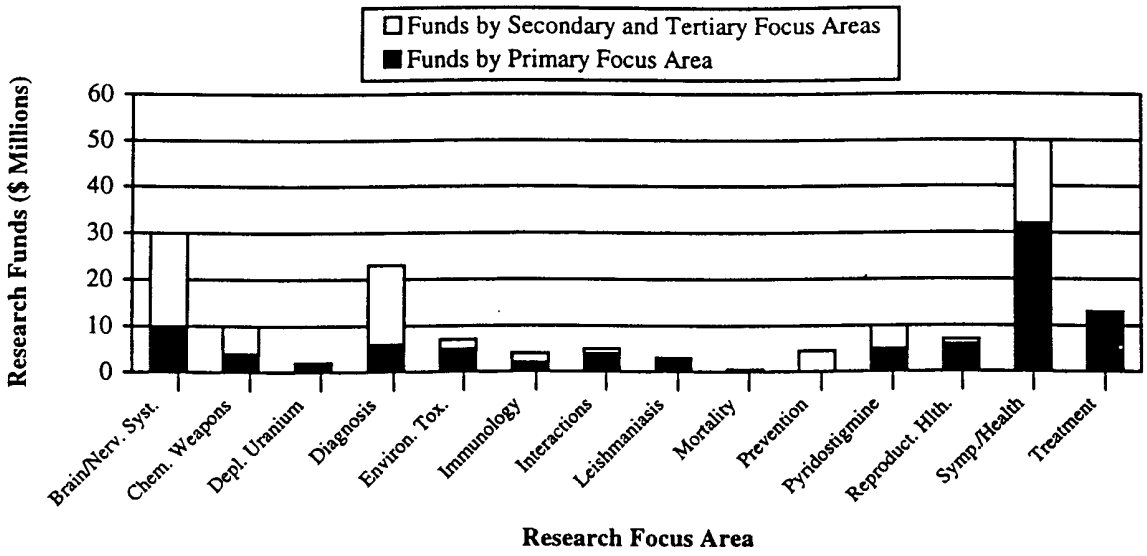

Figure 3. Research Costs by Research Focus Areas

The distribution of research projects across various research focus areas has changed over time since 1994 as a reflection of the evolution of issues centered on Gulf War veterans' illnesses. There has been a relatively greater increase over the years of research on chemical interactions, chemical warfare agents and pyridostigmine bromide. These increases are an outgrowth of increased concern over the health risks posed to veterans by exposures to multiple toxic agents at low levels. It is significant to note that of all potential etiologic agents, the largest investment is in research on chemical weapons.

In the future it is anticipated that there will be even greater emphasis on diagnosis, treatment, and planning for future deployments.

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Methodological Challenges in Epidemiologic Research on the Health of Gulf War Veterans

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When a well-defined hypothesis links an exposure to a health consequence, several research options are available; they include laboratory work to address mechanisms of toxicity and effects in experimental systems; randomized clinical studies of humans, if ethical and feasible; and observational epidemiologic studies. When the issue of interest is a complex, multifaceted experience, such as having served in the Persian Gulf War, rather than a well-defined exposure, it is epidemiology that assumes the predominant role. The only way to answer the global question of whether the health of veterans who served in the Gulf War has been altered as a consequence of that experience is through observational epidemiologic studies. However, the very complexity and ambiguity that force a reliance on epidemiology make the design and conduct of informative epidemiologic studies especially challenging.

Exposure is easy to identify at the level of having served in the Persian Gulf during the period of the conflict. Without greater specificity, however, a causal role of deployment is of questionable plausibility and scientific value. As the research question takes on greater resolution, the availability and quality of information on exposure are more limited. Assessing exposure to specific environmental agents, such as chemical weapons, toxic fumes from oil well fires, or psychological stress, requires more refined methods, and available data are inadequate.

If there is interest in an exposure encountered equally by all those who served–for example, high ambient temperatures–then the optimal design is to simply compare all war veterans with otherwise comparable persons who did not serve. Most suspected hazardous agents or experiences, however, are likely to have been unevenly encountered in the war, with some veterans more highly exposed (for example, to leishmaniasis) than other veterans, or some not exposed at all. If only a subset of veterans is exposed to a hazard, and we fail to isolate that subset of veterans for study, the observed association among all veterans will be diluted. The smaller the proportion of truly exposed veterans, the more likely the association is to be missed if we study veterans in the aggregate. Thus, studies of the health of Gulf War veterans in the aggregate provide little information on the chronic effects of leishmaniasis.

Varying levels of exposure among veterans also allow for examination of dose-response gradients, which are of great value in attempting to draw causal inferences. Finding a very small elevation in chronic respiratory illness among all veterans would be far less convincing of a causal association with oil well fires than would a gradient of increasing risk with increasing proximity and duration of exposure to those fires.

Finally, specifying exposure allows for experimental, laboratory research to address the hypothesized phenomenon. While we cannot simulate "the war experience" in the laboratory, we can study pesticide exposure or immunizations. The inherent limitations in observational epidemiology make convergent evidence from other approaches highly desirable.

Health outcomes concerns parallel those regarding exposure. The question of whether health has suffered from service in the Gulf War is too broad to be of much scientific value. While global measures such as mortality from all causes are readily measured, they are unlikely to be affected by service in the war. If, in fact, a subset of diseases or causes of death has been affected, and we measure a much broader aggregation, then the measure of association will be diluted and may not be recognized at all. Notation of a lack of increased mortality, for example, among veterans in the aggregate, provides little assurance that there are not subsets of veterans suffering from excess rates of specific illnesses.

As the hypothesized health effect is narrowed, our ability to detect associations improves. The more specific the health problem, the fewer extraneous determinants there are to consider as potential confounders, that is, disease determinants that happen to be associated with service in the Gulf War. If some pesticide encountered in the Gulf War resulted in symptoms like those of Parkinson's disease, we would expect to observe greater elevations in this illness than for illnesses in the aggregate. Even negative results, such as finding that such a set of symptoms is not increased among Gulf War veterans, have more value in evaluation of the consequences of military service.

Much attention has been focused on a unique syndrome related to service in the Gulf War. If such a syndrome existed and could be unambiguously identified, it would be readily detected through epidemiologic research. No persons who did not serve in the Persian Gulf War would have this syndrome, and some number of those who did serve would manifest it. With a rate of "0" for the unexposed, any occurrence in the exposed population would yield a relative risk of infinity.

Special challenges make it difficult to determine whether some aspect of the war experience has caused some adverse health outcome. The long list of difficult-to-measure exposures and health outcomes of concern is perhaps the greatest challenge. Whatever causal relations, if any, may link exposures to health outcomes, the time course must be considered. If there were acute, reversible effects of specific exposures, those would have been missed because the military personnel were not monitored during the war. If there are long-delayed manifestations of exposure, analogous to those associated with some carcinogenic agents, then insufficient time has passed for them to become apparent. Looking for adverse outcomes in the wrong time period will lead to failure to detect associations that are truly present.

A second issue is the problem of interpreting clinical data collected on those who seek medical care. The goal is to make inferences about whether exposures have adversely affected populations, but all that is known from clinical examination data is that those individuals have sought medical care for perceived health problems. Tabulations of information from these groups have little epidemiologic value. The chain of events from a biological problem to its perception and the seeking of medical care is convoluted, strongly affected by psychological, financial, and even political factors. Given substantial undiagnosed, untreated illness in the population, those who seek care and come to be diagnosed are a distinctly nonrandom subset of all those affected. Risk factors for seeking or obtaining care may well be misinterpreted as risk factors for illness, and the tendency to seek care may well be related positively or negatively with service in the Gulf War. The question is not whether those who seek care are ill or whether they deserve treatment; those are clinical and ethical questions, respectively, not epidemiologic ones. The epidemiologic question is whether at least some ill individuals would not have been ill had they not served in the Gulf War, requiring a comparison of illness rates in exposed versus unexposed persons.

Tabulations of clinical examination results do have some applications. First, they can help to suggest conditions that should be systematically evaluated in population-based surveys. Given the diversity of potential exposures and outcomes, such guidance is of real value. Second, they can determine a minimal rate of occurrence for diagnosed conditions. So long as the population at risk can be enumerated, the number of self-referred, diagnosed cases provides a minimum estimate of the frequency of the condition.

A challenge in any observational epidemiologic study is the isolation of the exposure of interest from other associated exposures or conditions that may influence the health outcome. Efforts to compare the health of veterans to that of nonveterans is predicated on baseline comparability of the two groups. In principle, had the veterans not been deployed (a condition we cannot observe directly), they would have experienced the rates of illness and death experienced by the veterans who in fact were not deployed. Similarly, in comparing subgroups of deployed veterans with varying exposures, i.e., those who were and were not exposed to the oil well fires, we would like to believe that the groups are comparable. The optimal approach to making such inferences is through randomization of exposure; the closer we get to having random allocation naturally, the stronger the epidemiologic inferences. In order to address this

question in Gulf War veterans, the basis for assignments must be scrutinized to determine whether, through overt or subtle means, those who served in the war or were exposed to particular hazards were especially prone to, or resistant to, diseases of concern.

Susceptibility to disease subsequent to any exposure varies markedly in the population. Through genetic or other environmental factors, the effects of a given hazardous exposure vary. The current revolution in human genetics promises to help in unraveling some genetic determinants of inter-individual variation in susceptibility. When such variation is not measured or recognized, we assess the average risk to the population. If we were able to isolate those persons who are more susceptible, they would show large relative risks; whereas, the subset of the population that is not susceptible at all would experience no increase. This concept applies to susceptibility to chemical agents as well as stress – not all those who were chosen to serve in the war began as equally vulnerable. Efforts to determine, for example, whether those in the reserves were especially susceptible to adverse health consequences may be of value.

Application of epidemiology to public policy is always challenging, especially in such a politically sensitive arena as the health of Gulf War veterans. Because the concerns are global (some war-related exposure causing some adverse health experience) and the available data are of limited quality, conclusive evidence will remain elusive. A reasonable goal for epidemiologic research is to narrow the range of possibilities. Current evidence renders a universal, readily measured, prolonged adverse health effect from service in the Gulf War highly unlikely, but effects on subgroups of veterans with specific exposures, subtle or complex health problems, and transient or long-delayed problems may well have occurred. The optimal public policy in response to that evidence is a challenge that goes well beyond epidemiology or scientific evidence more generally.

Nosologic Challenges of Diagnostic Criteria for a "New Illness"

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With the technologic advances of the 19th and 20th century, many old ailments that had been named clinically as a dis-ease (a discomforted ease) were converted to "new" diseases that were identified morphologically or with laboratory tests. Thus the old jaundice became the new hepatitis; and the old angina pectoris became the new coronary artery disease. With further advances in microbiology and technology, new levels of causation were recognized and new nosologic entities appeared, such as hepatitis C virus and hypercholesterolemia.

These new morphologic and laboratory entities led to major nosologic and diagnostic problems because the diverse spectrums of clinical, morphologic, and laboratory entities were not always uniquely associated. Someone with angina pectoris might not have coronary disease, and someone with coronary disease might not have hypercholesterolemia. Similarly, jaundice might occur without hepatitis, or the hepatitis might not be hepatitis C. During the nosologic disputes of the 19th century, when old clinical ailments received new morphologic titles, Jean Charcot, a prominent clinician of that era, argued that "Disease is very old and has not changed. It is we who change as we learn to recognize what was formerly imperceptible."

These new perceptions may make an old ailment become falsely regarded as new. Among the reasons for this confusion are the availability and use of the identifying technology, and the opportunity for disease dissemination provided by modern travel and patterns of behavior. A third source of confusion – which does not create new diseases, but dramatically increases the frequency of old ones – is the increased longevity made possible by the conquest of infections and other diseases that were formerly lethal in infancy or relative youth. People now live long enough not only to develop senile dementia and diverse cancers but also to receive the screening tests that discover many cancers that were previously unsuspected premortem.

In the midst of all these nosologic and technologic advances, however, certain symptoms and clinical manifestations have regularly continued to occur without being explained by any accompanying overt pathophysiologic or objective abnormalities. Among these manifestations are the following: chronic fatigue or lassitude; impaired cognition (with problems in attention, memory, reasoning, or concentration); arthralgia and/or myalgia; sleep disturbances; headache and or dizziness; nausea; chest pain; and shortness of breath.

These manifestations can appear in various combinations and clusters. The individual constituents of the clusters may not be the same from one person to the next, but their concurrent "running together" is often labelled as a syndrome. People who have this syndrome are often greatly distressed about it but are seldom in objectively poor health. The onset may be gradual and chronic, or relatively sudden and acute; but regardless of the developmental pattern, the syndrome is difficult to cure, and may last for long periods of time. Persistence of the syndrome is frustrating for physicians, who often order huge numbers of tests that fail to provide an etiologic explanation, and also for the patients, who wonder why a cure evades the many miracles of modern medicine. People with the syndrome often go back and forth from one physician to another, or to diverse practitioners of alternative medicine. When the syndrome occurs in groups of people, a search begins for something to blame.

One particular stimulus that has regularly been followed by this syndrome and then blamed for it has been war. According to Hyams et al., the syndrome was noted in the U.S. Civil war and was called "irritable heart syndrome" by DaCosta. The same syndrome, occurring in World War I, was called "neurocirculatory asthenia" in the United States and "effort syndrome" in Britain. In World War II and in the U.S.-Korean war, the effort syndrome recurred and was attributed to "acute combat stress reaction." In the U.S.-Vietnam war, the syndrome was at first called "post-traumatic stress disorder" but was later

attributed to exposure to the herbicide Agent Orange. More recently, after the Persian Gulf war, the syndrome has reappeared and is called the "Gulf War Syndrome."

The features that seem to constitute this syndrome do not require exposure to war, however. In recent years, the syndrome has been attributed to exposure to Lyme Disease, and in women who received silicone breast implants, it has been called the "Siliconosis Syndrome." The syndrome has also appeared after allegedly toxic exposures to a "sick building," "multiple chemicals," or "sour gas" from a refinery, or to ingestion of an allegedly contaminated tryptophan dietary supplement.

Fortunately, my assignment at this conference is not to try to explain the reasons why so many people develop the syndrome, or why it can arise from such diverse etiologic exposures. Instead, I have been asked to discuss the nosologic challenges of diagnostic criteria for a "new illness." I hope that my discussion can avoid involvement in the sociopolitical toxics and land mines that appear whenever the Gulf War Syndrome has been studied.

The first step in investigating a new illness, of course, is to demonstrate that the illness itself is indeed new. If, by "illness," we mean clinical manifestations – such as headache, fever, fatigue, warts, lumps, swollen joints, or muscle aches – the task is particularly daunting because almost no clinical manifestations are truly new. Just about everything that can be observed at the bedside to examining room has been observed before. What is usually new is a particular technologic test that demonstrates the concurrence of such entities as eosinophilia, or low CD-4 cell counts as laboratory manifestations of the illness. A laboratory test can also suggest a new etiologic agent, such as HIV infection of the *Legionella* bacterium.

Unless the alleged etiologic agent can be shown in each case, however, the ailment should initially receive an alternative label, which indicates the apparent locations or characteristics of the apparent "common source outbreak" without identifying a "cause." Thus, the term Gulf War Syndrome denotes a geographic attribute, and Eosinophilic Myalgia Syndrome denotes a particular laboratory attribute. (Even the geographic name is not always satisfactory, however. Lyme Disease has now been found in many places other than the region near Lyme, Connecticut.)

A particularly unfortunate custom is to name the disease after an alleged etiologic agent that has not yet been unequivocally proved. For example, several generations of modern physicians were taught that ulcers in the stomach and duodenum were called peptic ulcer, even when an elevated "peptic" acid was absent. The unsatisfactory nomenclature delayed, for almost a century, a suitable search and subsequent recognition of the helicobacter etiologic agent.

The next step is to set up an initial set of diagnostic criteria for the disease. The criteria need not be perfect; they can always be improved later. They are crucially needed, however, identifying cases that can help indicate the frequency and scope of the disease. If the criteria are well-defined, they may initially cover only part of the spectrum of the disease; and the spectrum (and diagnostic name) may later be expanded or changed. Examples are Lyme Arthritis, which later became Lyme Disease, and Gay Bowel Disease, which later became part of AIDS and perhaps part of the hepatitis C disease.

The "definitive" criteria themselves can be constructed in several ways: as a minimum count of constituent elements (as in Systemic Lupus Erythematosus), as a minimum sum of weighted scores for different elements (as in several rheumatic vasculitides), as clustered patterns of elements (as in Rheumatic Fever), or in other methods. The criteria must have two crucial distinctions, however, as follows.

1. They should not include any suspected etiologic entity unless that entity has already been shown to be present in all cases. Without this precaution, the disease cannot be diagnosed if the etiologic entity is absent. For example, because the facial deformities of the so-called fetal

alcohol syndrome can occur in the absence of preceding alcohol intake, the disease has not been well-named. Similarly, if L-tryptophan intake were required for a diagnosis of Eosinophilic Myalgia, cigarette smoking for lung cancer, or diethylstillestrol for clear-cell cancer of the cervix or vagina, none of those diseases could be identified when they occur – as they often do – in the absence of the alleged etiologic agent.

2. After enough cases have been identified, the diagnostic criteria should promptly be checked for suitable reproducibility and accuracy. For testing accuracy, a "gold-standard" set of cases and noncases should be assembled, from a consensus of experts who are not using the criteria. The noncases in this set should not be composed of "healthy, normal" persons. Instead, the noncases should contain conditions that may clinically resemble the new "index" disease. Otherwise, the diagnostic criteria will not be suitably challenged in the ability to discriminate the "new" disease from other conditions that may occur in a clinical masquerade. Thus, it is easy to separate Lupus Erythematosus from normal. The challenge is to separate it from rheumatoid arthritis or other pertinent ailments. After a suitable set of cases and noncases has been assembled, the performance of the criteria should be checked against the gold standard challenge set.

I am not aware of suitable testing of diagnostic criteria proposed for Gulf War Syndrome or for another highly controversial entity – the so-called Siliconosis Syndrome, which has the additional flaw of incorporating the alleged etiologic into both title and constituent entities. Scientific progress as well as sociopolitical satisfaction will be delayed in finding a cause and suitable treatment for these ailments until they have met the most elemental requirements for demonstrating that they exist as distinct nosologic entities.

Overlapping Syndromes

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Observant physicians over the years have noted that there are numerous clinical conditions that share features such as fatigue or pain and other symptoms in the absence of objective findings, disability out of proportion to physical findings, and a marked association with "stress" and psychosocial factors. Often labeled "psychosomatic" or "functional" disorders, they include relatively commonly encountered illnesses such as chronic fatigue syndrome (CFS), fibromyalgia (FM), irritable bowel syndrome (IBS or "spastic colon"), and temporomandibular disorder (TMD), as well as chronic tension headaches, post-concussion syndrome, interstitial cystitis ("spastic bladder"), multiple chemical sensitivities, chronic pelvic pain, chronic nonbacterial prostatitis, and chronic low back pain. Despite the multiplicity of diagnostic labels, we believe these conditions represent "overlapping" syndromes. That is, the diagnostic label assigned to patients with one of these conditions is likely to depend more on their chief complaint and the type of physician making the diagnosis than on the actual illness process. However, the overlap is seldom identified as both patient and provider concentrate on determining the cause for the primary symptom. Not unexpectedly, patients with such conditions consume enormous resources in their search for good health.

The existing data, though limited, suggest that these illnesses are similar, if not identical conditions. For example, chronic, debilitating fatigue is common in FM (1-3) and 21%-70% of patients meet criteria for CFS (1,3,4). In addition, 52% -70% of patients with FM report symptoms of IBS when explicitly queried (4-6). Conversely, 65% of IBS patients meet strict criteria for FM (6), and over half report "constant tiredness," as well as symptoms compatible with interstitial cystitis (7). In a study of patients with CFS, FM, and multiple chemical sensitivities, over 80% of each group had debilitating, chronic fatigue. Over 70% of FM patients and 30% of those with multiple sensitivities also met the case definition of CFS, and half of CFS and FM patients reported environmental sensitivities (1). Lastly, 70% of CFS patients have FM on examination (8).

To determine the nature and extent of the overlap between CFS, FM, TMD and other disorders, we assessed patients diagnosed with one of these three conditions and healthy clinic patients for the presence of the 10 "overlapping" conditions. To accomplish this objective, the measures described below were administered to 25 patients with each of the following illnesses (N = 100): FM, CFS, TMD and 25 healthy control subjects. Patients were recruited from medical clinics at the University of Washington and Harborview Medical Center (Chronic Fatigue, Rheumatology, Oral Medicine). Patients with underlying medical conditions such as renal or hepatic disease, endocrine or auto-immune disorders, chronic infections conditions, malignancies, or drug abuse were excluded. Control subjects were 25 healthy individuals seen in the Dermatology Clinic for minor skin problems.

Study measures included self-report questionnaires, an interview with a physician, and a physical examination. Questionnaire consisted of a Symptom Checklist, which listed symptoms characteristic of each of the 10 "overlapping" syndromes. When a formal definition existed (e.g., CFS, TMD, IBS, tension-type headache), it was incorporated into the questionnaire. However, for some of the study conditions criteria have not yet been established. In these cases, a panel of at least two medical experts designed questions by consensus to capture the salient features of the condition. Subjects were also asked if they has ever been diagnosed by a physician with any of these conditions. Lastly, a physical examination with palpation of the 18 musculoskeletal sites specified by the criteria for FM was performed by a physician. The results are shown in Table 1:

Table 1. Percentage of Patients Reporting Overlapping Conditions Diagnosed by a Physician

Self-reported Diagnoses	CFS (n=25)	FMS (n=22)	TMD (n=25)	Controls (n=22)	p Value
CFS	100	18.2	0	0	≤ .00001
FMS	80	100	9	0	≤.00001
TMD	28	24	88	14	≤ .00001
IBS	36	59	16	0	≤ .0001
Interstitial cystitis	8	8	17	0	ns
Tension headache	4	23	36	0	≤ .01
Post-concussion syndrome	8	0	0	0	ns
Multiple chemical sensitivity	4	18	0	0	≤ .05
Chronic pelvic pain	8.3	18	8	0	ns
Chronic low back pain	32	67	16	18	≤ .001
Mental health problem	64	86.4	44	9.1	≤ .00001

Table 2 shows the mean number of symptoms for each diagnosis (based on either a formal or expert panel definition) reported by patients with CFS, TMD and FM.

Table 2. Mean Number of Symptoms for Clinical Syndromes Defined by "Expert" Practitioners

Syndrome	# Symptoms	CFS	TMD	FMS	Controls	p Value
CFS	12	11.0	5.2	8.6	1.0	≤ .001
TMD	25	11.6	16.0	14.6	9.3	≤ .01
FMS	6	5.2	3.2	5.0	0.4	≤ .001
IBS	7	5.3	3.8	4.9	1.5	≤ .001
Interstitial cystitis	5	1.1	0.7	1.6	0.6	≤ .05
Tension headache	4	2.2	2.2	1.7	0.1	≤ .001
Post-concussion	5	4.3	2.5	4.3	0.7	≤ .05
Multiple chemical sensitivity	21	14.5	13.0	15.5	4.3	≤ .05
Chronic pelvic pain	22	12.9	11.8	10.8	15.8	ns
Low back pain	11	3.6	2.4	5.8	1.4	≤ .001

For those syndromes with formal case definitions, we found a high number met the Rome criteria, but few qualified for the International Headache Society diagnosis of tension-type headache. See Table 3.

Table 3. Diagnostic Classifications

Diagnosis	Criteria	CFS	TMD	FMS	Controls	p Value
CFS	1994 CDC	100%	20%	64%	0	≤ .00001
FMS	1990 ACR	20%	13%	71%	0	≤.00001
IBS	1992 Rome	92%	64%	77%	18%	≤ .00001
Tension-type headache	1988 IHS	12%	8%	5%	0	ns

Finally, as expected those with FM had the most tender points (by definition), but all groups had a significantly greater number of mean tender points than the controls. These findings are similar to hose previously published. See Table 4.

Table 4. Tender Point Count by Diagnosis

CFS	TMD	FMS	Controls	p Value
7.4	5.2	11.0	0.9	<.001*
	6.3	11.4		<.001**

* FMS > CFS, TMD, Controls, $p \leq .01$

** Plesh, Wolfe & Lane, 1996 (TMD = 99, FM = 30)

In addition to these demographic and clinical similarities, psychosocial factors appear to play an important role in these illnesses. Although we lack formal comparative studies of any "overlapping" illnesses, affective, anxiety, and somatoform disorders may be exceptionally common (4, 9-11). This literature also suggests that at least in some patients, for example those with IBD (12), FM (13), and chronic pelvic pain (10), occult histories of domestic violence and sexual abuse may be highly prevalent and complicate diagnosis and treatment. In addition, several studies have demonstrated that stressful and traumatic life events, psychological distress, and psychiatric disorders may be associated with both immune system impairment and "activation" (14, 15). In summary, more research is needed to further characterize the degree of overlap and to establish the underlying, likely similar, pathophysiology for these disorders.

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Symptoms in Gulf War Veterans and the General Population

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Physical symptoms account for over half of all outpatient visits -- an estimated 400 million clinic visits each year in the United States alone. Four of the most common symptoms reported by Gulf War veterans[1] -- fatigue, joint pains, headache, and sleep complaints -- are very prevalent in the U.S. population as a whole. In this context, it is useful to compare symptom prevalence in Gulf War veterans with published data from three civilian surveys -- two surveys of patients presenting for medical care to outpatient clinics, and one survey done with persons in the general population not seeking health care.[2-4] In these three studies, fatigue was a problem for 22%-58% of respondents; joint pains for 26%-59%; headaches for 21%-37%, and sleep complaints for 15%-35%. Also very prevalent in these surveys were dyspnea (14%-32%), and abdominal pains (11%-24%). The frequency of these particular symptoms in the general clinic population (and very prevalent in Gulf War Veterans evaluated in our Program) is further confirmed by examining data from the National Ambulatory Medical Care Survey (NAMCS). This national sample of clinics in the United States reported that in 1989, the number of outpatient visits in the United States for fatigue was estimated to be 7 million; for headaches, 9.6 million; for joint pains, 17 million; for skin rash, 14 million.

In approximately one out of three patients presenting with a physical symptom, a precise physical cause of the symptom cannot be identified even after medical evaluation.[4-6]

It is common for many patients to experience more than one symptom. Four separate studies have shown that on symptom checklists, typical outpatients will endorse a median of four symptoms as bothersome, with one-third of patients complaining of zero-one symptom, one-third two to three symptoms, and one-third four or more symptoms.[2,4,6,7] Part of this may be due to the fact that many symptoms are common episodic experiences -- fatigue, headaches, a sore back or neck or shoulder, gastrointestinal disturbances, trouble sleeping -- and that when given checklists persons will check all symptoms that have been noticed, allowing the physician to decide on what needs further evaluation. Indeed, concern or worry about what a symptom means or signifies has been shown to be a powerful determinant of seeking health care for physical symptoms. The potential or perceived seriousness of a symptom (Could this chest pain represent heart disease? Could this dizziness be a warning of circulation problems or a stroke? Could this abdominal pain be a sign of cancer?) is as much of a reason to report symptoms to a health care provider as the actual severity of a symptom.

Extensive research has revealed that it is also important to inquire about the possibility of depression or anxiety disorders in patients with multiple or unexplained physical symptoms. Many studies have documented that these conditions are very common in primary care, existing in one out of every four patients presenting for care in the outpatient setting, and in at least half of patients who report multiple or unexplained symptoms.[4,8]

It is important to emphasize that just because depression or anxiety frequently coexists in patients with unexplained or multiple symptoms, this doesn't mean that they cause the symptoms. It is possible that in some patients persistent unexplained symptoms may lead to feelings of depression or anxiety. It is also possible that depression or anxiety lowers the tolerance to common physical symptoms or that neurotransmitter imbalances associated with depression and anxiety states produce changes in energy, sleep, pain thresholds, and gastrointestinal function. Whether a cause or a consequence, however, there is some evidence that treatment and alleviation of depression or anxiety when they are present can alleviate some of the impairment or suffering related to unexplained physical symptoms.

Finally, "symptom syndromes" (i.e., illnesses manifested solely by combinations of symptoms with a paucity of objective findings on physical examination or laboratory testing and for which an adequate cause is yet to be determined) are common in clinical practice and the general population, including

entities such as irritable bowel syndrome, fibromyalgia, chronic fatigue syndrome, premenstrual syndrome, and other conditions. Moreover, the overlap among specific symptom syndromes is substantial. Many patients with one syndrome also suffer from one or more of the other syndromes as well.

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Factor Analysis and Related Methods in Epidemiological Research

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Because factor analysis has been used in a number of studies to define the Gulf War Syndrome, I have been asked to comment on the use of factor analysis in this context.

First let me describe what factor analysis is. Factor analysis is a technique originally developed by psychologists for discovering hypothetical variables that explain the correlations among a set of observed variables by making the observed variables into weighted linear functions of the hypothetical variables (Mulaik, 1972). To illustrate, in personality studies psychologists frequently begin with ratings of numerous individuals on a number of rating scales made by a large sample of raters. For example each rater may have a set of scales to rate his or her individual on:

1. FRIENDLY: _1_:_2_:_3_:_4_:_5_:_6_:_7_:UNFRIENDLY
2. SYMPATHETIC: _1_:_2_:_3_:_4_:_5_:_6_:_7_:UNSYMPATHETIC
3. KIND: _1_:_2_:_3_:_4_:_5_:_6_:_7_:CRUEL
4. AFFECTIONATE: _1_:_2_:_3_:_4_:_5_:_6_:_7_:UNAFFECTIONATE
5. INTELLIGENT: _1_:_2_:_3_:_4_:_5_:_6_:_7_:UNINTELLIGENT
6. CAPABLE: _1_:_2_:_3_:_4_:_5_:_6_:_7_:INCAPABLE
7. COMPETENT: _1_:_2_:_3_:_4_:_5_:_6_:_7_:INCOMPETENT
8. SMART: _1_:_2_:_3_:_4_:_5_:_6_:_7_:STUPID
9. TALKATIVE: _1_:_2_:_3_:_4_:_5_:_6_:_7_:UNTALKATIVE
10. OUTGOING: _1_:_2_:_3_:_4_:_5_:_6_:_7_:WITHDRAWN
11. GREGARIOUS: _1_:_2_:_3_:_4_:_5_:_6_:_7_:SOLITARY
12. EXTRAVERTED: _1_:_2_:_3_:_4_:_5_:_6_:_7_:INTROVERTED
13. HELPFUL: _1_:_2_:_3_:_4_:_5_:_6_:_7_:UNHELPFUL
14. COOPERATIVE: _1_:_2_:_3_:_4_:_5_:_6_:_7_:UNCOOPERATIVE
15. SOCIABLE: _1_:_2_:_3_:_4_:_5_:_6_:_7_:UNSOCIABLE

After each individual is rated, we may compute the correlation coefficients between each pair of rating scales and arrange them in a "correlation matrix" as shown below:

	1 FRIENDLY														
1. FRIENDLY:	1.000	2 SYMPATHETIC													
2. SYMPATHETIC:	.7771	.000	3 KIND												
3. KIND:	.809	.8691	.000	4 AFFECTIONATE											
4. AFFECTIONATE:	.745	.833	.8351	.000	5 INTELLIGENT										
5. INTELLIGENT:	.176	.123	.123	.1121	.000	6 CAPABLE									
6. CAPABLE:	.234	.159	.205	.183	.7911	.000	7 COMPETENT								
7. COMPETENT:	.243	.155	.187	.186	.815	.8651	.000	8 SMART							
8. SMART:	.234	.190	.238	.215	.818	.841	.8151	.000	9 TALKATIVE						
9. TALKATIVE:	.433	.319	.321	.435	.174	.209	.239	.2581	.000	10 OUTGOING					
10. OUTGOING:	.473	.480	.410	.527	.220	.274	.269	.261	.7441	.000	11 GREGARIOUS				
11. GREGARIOUS:	.433	.438	.406	.526	.188	.227	.242	.228	.711	.8531	.000	12 EXTRAVERT			
12. EXTRAVERT:	.447	.396	.350	.500	.192	.221	.227	.224	.758	.846	.8011	.000	13 HELPFUL		
13. HELPFUL:	.649	.693	.697	.694	.283	.344	.370	.365	.443	.552	.514	.4731	.000	14 COOPERATIVE	
14. COOPERATIVE:	.662	.692	.676	.679	.311	.345	.375	.351	.431	.557	.514	.493	.7401	.000	15 SOCIABLE
15. SOCIABLE:	.558	.543	.510	.632	.213	.289	.287	.745	.886	.820	.830	.631	.6261	.000	

SYMMETRIC MATRIX
LOWER HALF SHOWN

Then we subject this correlation matrix to a somewhat complex mathematical process that creates and extracts from the correlations a set of factor loadings on some hypothetical factors that are common to several of the rating scales:

	Factor			
Scale	1	2	3	4
1. FRIENDLY	.863	.029	.043	-.010
2. SYMPATHETIC	.860	-.029	.008	.061
3. KIND	.939	.024	-.087	.022
4. AFFECTIONATE	.742	-.021	.138	.064
5. INTELLIGENT	-.035	.889	-.001	.012
6. CAPABLE	.052	.918	.030	-.062
7. COMPETENT	-.074	.868	-.011	.127
8. SMART	.061	.908	.001	-.024
9. TALKATIVE	-.016	.006	.775	.028
10. OUTGOING	-.008	.018	.929	.031
11. GREGARIOUS	.019	.012	.897	-.020
12. EXTRAVERT	.030	.000	.926	-.061
13. HELPFUL	.028	.017	.012	.797
14. COOPERATIVE	.057	.018	.032	.765
15. SOCIABLE	.027	-.004	.790	.178

Four factors were found for the 15 scales and the loadings of the 15 scales on the four factors are shown in the above table. To interpret a factor, you go down the column corresponding to the factor and look for "loadings" on the factor that are large relative to those that are near zero. Whatever you think is common to the variables having large loadings can be your interpretation for the factor. For example, we note that the scales FRIENDLY, SYMPATHETIC, KIND, and AFFECTIONATE all have "high loadings" on Factor 1. The other scales have near zero loadings on this factor. So, we might regard this factor as "friendliness." Similar inspections of the other columns would yield interpretations of "ability," "extraversion" and "helpfulness" for the other three factors. Also helpful in interpreting a factor are the correlations among the factors reported by the factor analysis:

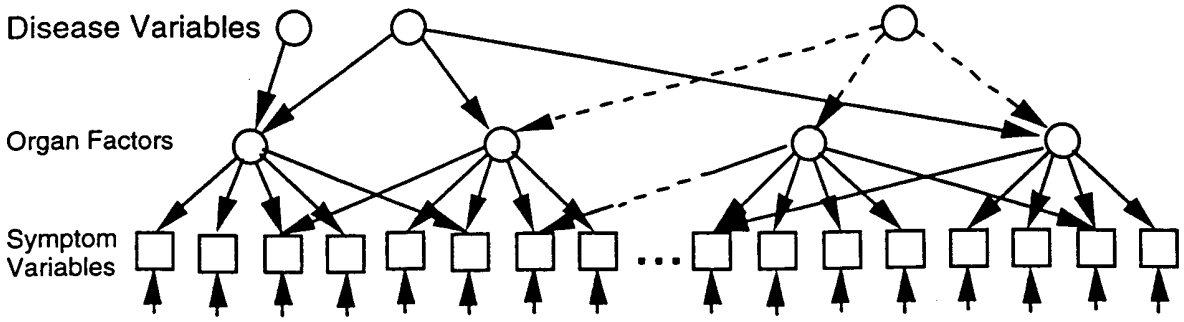
	1 FRIENDLINESS			
1. FRIENDLINESS	1.000	2 ABILITY		
2. ABILITY	.202	1.000	3 EXTRAVERSION	
3. EXTRAVERSION	.515	.263	1.000	4 HELPFULNESS
4. HELPFULNESS	.882	.428	.660	1.000

We note that "friendliness" has low correlations with "ability," a moderate correlation with "extraversion" and a strong correlation with "helpfulness." Helpfulness seems to have something in common with the other three factors. You have to be friendly, able and involved with people to be helpful. But that might not be enough to make you helpful or not, so, the distinctness of "helpfulness" may represent an added ingredient that is more than the other three factors. Because the factors are correlated, there is the possibility that there exist factors common to these factors that explain their intercorrelation. These are known as "second-order" factors and they are found by factor analyzing the correlations among the first-order factors.

That illustrates what factor analysis does. We could apply it to almost any kind of content as long as we can safely assume that the variables we study are linear functions of certain hypothetical common factors. In medical settings the variables might represent symptom *variables*, representing different degrees of some symptoms. The factors would be whatever might be the most immediate common causes of the variation among the symptoms and this might make factor analysis problematic for epidemiological studies.

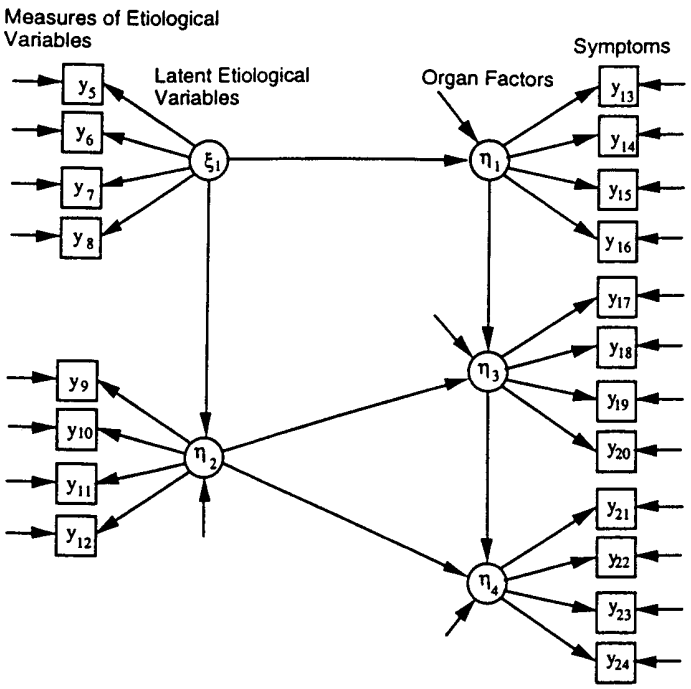
Most frequently the presenting symptoms are themselves functions of the functioning of internal organs, and so the common causes of diverse symptoms may be the variation in function of some organ or group of organs. So, as long as there is variation in levels of functioning of internal organs, this may manifest

itself in correlated symptoms that all depend on the same organs. But symptoms are not always univocal. Some symptoms may depend on several organs, so the relations of symptoms to organ functioning may be complex. But aside from that, in most patient populations you will have variation in symptom variables that reflects the usual variation in organ functioning produced by numerous diseases. The factors to be revealed are just the organ functioning factors. They may not ordinarily reflect specific disease syndromes. In fact, factors are not syndromes—which are defined by values or ranges of values on certain variables. Factors are variables. But to the extent that a disease represents dysfunction of a given organ system, it might be reflected in symptom variables that depend on the level of functioning of that organ system. Still more than one disease can similarly affect the same organ groups, producing variation in their function and similar symptom patterns. So, the factors need not be univocal indicators of disease agents either. In fact, the presence and absence of a disease agent represents a common causal variable somewhat removed from the more immediate causes of symptoms in the varying function of organs. This means that while one will find factors of organ functioning in the correlations among symptoms, you will not have direct indicators of the causes of the variation in organ functioning. So, factor analysis will not reveal the agents of disease. Still, can factor analysis reveal the presence of a disease variable as the common cause of some new strange pattern of symptoms? Only if the disease variable affects the organ systems in some new way, and I would suggest at a second-order factor level:



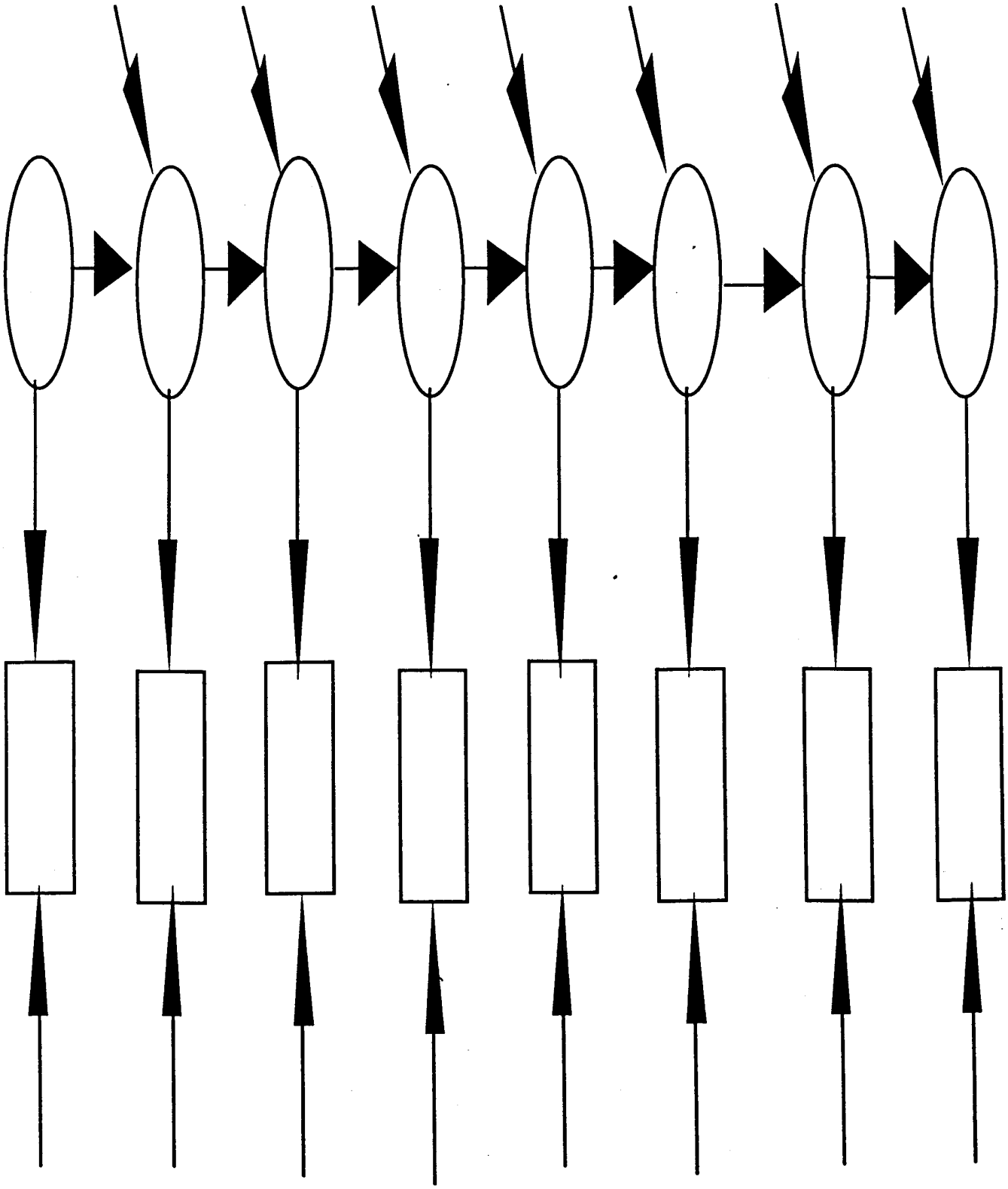
Furthermore, any disease variable that affects only one organ system will be confounded completely with a first-order factor and not show up except in the form, say, of a greater variance for the first-order factor. So, to appear as a distinct disease variable second-order factor, the disease variable would have to influence at least three organ symptoms and in a way distinct from the influence of other disease variables on the organ systems of the body. But the situation is likely further complicated because of interdependencies among the organs themselves.

The major problem of factor analysis of symptoms alone is that one lacks measures of the etiological agents. One can treat the etiological variables as exogenous and the organ factors, symptoms and measures of etiological agents as endogenous. Which brings me to structural equation modeling, which is a merger of path analysis and factor analysis (cf. Jö reskog, K. G. & Sö rbem, D. 1979).



Structural equation modeling, however, is not an exploratory technique, but a confirmatory technique. A researcher builds a model of how certain hypothetical variables are causally related and seeks confirmation of the model in its ability to reproduce the covariances among the observed variables. The corresponding exploratory technique would be multivariate multiple regression or a multivariate general linear model. The important thing is to include both measures of etiological agents and symptoms in the study. Structural equation modeling can be used in an exploratory way, by including paths with free parameters from each etiological latent variable to each of the latent organ factor variables. It will nevertheless be important to already have a well-developed model of the relations among the endogenous organ factors, something that is now lacking.

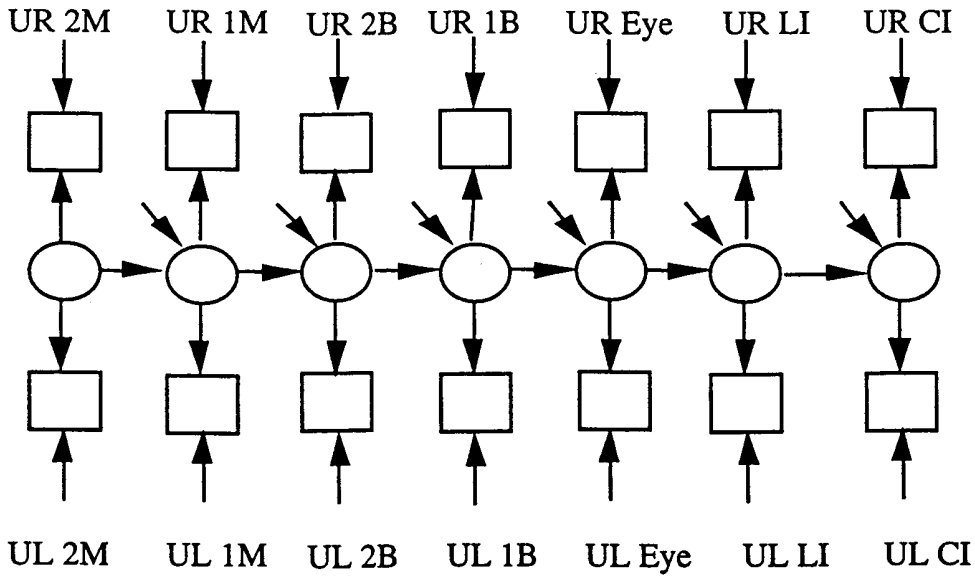
Structural equation modeling is more flexible than factor analysis, being able to model ordered relations between latent causes in time or space. A classic example is the simplex model that follows:



Variables are ordered in time or space. The correlations diminish between variables that are farther apart in the ordering:

$$\begin{bmatrix} 1.00 & & & & & & & \\ .74 & 1.00 & & & & & & \\ .71 & .82 & 1.00 & & & & & \\ .69 & .78 & .83 & 1.00 & & & & \\ .62 & .74 & .79 & .80 & 1.00 & & & \\ .59 & .68 & .72 & .74 & .77 & 1.00 & & \\ .57 & .66 & .72 & .72 & .73 & .74 & 1.00 & \\ .56 & .64 & .71 & .71 & .72 & .73 & .79 & 1.00 \end{bmatrix}$$

M. B. Jones (1960) reported a bisimplex model that fit correlations between measures of dental caries in each of the teeth of the mouth. In this model, not only is the degree of dental caries in adjacent teeth more highly correlated than that of teeth farther apart, but corresponding teeth on the opposite side of the mouth are also more highly correlated, suggesting that not only spatial position but function of the tooth is important to caries formation.



-- M. B. Jones (1960). *Molar Correlational Analysis.*

We would expect similar simplex patterns between measures of organ functioning of organs arranged either spatially or in terms of their physiological interconnections which may be ordered in time. The point to be made, as was made by Jones (1960), was that exploratory factor analyses of correlations among variables generated by such causal structures do not reveal the true complex relationships among them. A factor analysis of simplex data will return two or three common factors, when many latent variables are required. And the factors produced will not always be very meaningful. The physiological interconnectedness of the organ systems of the body is complex and will complicate the study of symptom correlations in the search for common causes.

Recommendations

If you insist on doing factor analysis, or structural equation modeling, then I have a number of recommendations:

(1) Develop a fine-grained selection of symptom measures of the diverse organ systems believed relevant to one's analysis. (2) Study symptom relations in typical groups to develop baselines for detecting differences in special groups in special circumstances. (3) Do comparative studies. Current factor analytic and structural equation modeling methods allow for comparisons between groups based on analyses within separate groups. In the present context that means, don't just study Gulf War veterans, but compare them with comparable cohorts who were not in the Gulf War. (4) Use structural equation modeling as knowledge-base develops, allowing one to formulate and test causal hypotheses. (5) Use structural equation modeling with both symptom measures and etiological measures in your models.

Some special comments on doing exploratory factor analysis: (1) Do common factor analyses instead of principal component analyses. (2) Don't always rely on the screen test or the "eigenvalues greater than 1" rule to determine the number of factors. These tend to take too few factors. (3) Rotate to oblique simple structure rather than orthogonal simple structure, so that you will have a basis for conducting second order analyses on correlations among factors.

Other techniques that may be of some use in discovering syndrome patterns are (1) cluster analysis, (2) neural net pattern recognition algorithms, (3) discriminant analysis wherein groups that vary in their exposure to certain situations are compared to discover linear combinations of their means on which the groups differ.

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Exposure and Exposure-Response Relationships

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It has been said that the three most important principles of environmental epidemiology are (in order of importance): exposure assessment, exposure assessment, and exposure assessment (C. Poole, personal communication to the author). We discuss various aspects of this important topic, with particular reference to Persian Gulf War (PGW) epidemiology.

We begin with defining exposure itself, a necessary step because it is a term that is used in various ways in various contexts. For our purposes, "exposure" is an event that occurs at the boundary between a human receptor and the environment, involving a specific concentration of a contaminant or agent for an interval or point in time. Exposure units thus involve concentration and time, e.g., 3 $\mu g/m^3$ in air of PAH on March 11, 1991. But multiple definitions of "exposure" exist and it is wise to be clear about which you are using or which is being used by others.

If we integrate (add up) exposure over a period of time we arrive at cumulative exposure, a combined measure of exposure and duration. Dose is the amount of contaminant absorbed or deposited during an increment of time, while internal dose is the amount absorbed into the body in an increment of time. Biologically effective dose is the amount of biologically active material presented to a relevant biological target within the body. A particular kind of dose expression, "burden," is the amount of substance that exists in body at a point in time. It may be expressed for the entire body, or for a single organ or tissue and can change over time, i.e., is a dynamic quantity that depends on prior cumulative exposure and the persistence of the substance in the body.

Exposures and doses come in varying states of resolution and quality. Roughly speaking, typically encountered forms can be arranged in a hierarchy of increasing quality, although in some circumstances a form higher on the list might be of more use or value than something beneath it:

Hierarchy of Exposure/Dose "Quality"

- Proportion of population exposed (probability of exposure)
- Exposed/not exposed
- Ordinal (e.g., low, moderate, high)
- Area (ambient) measurements
- Personal measurements
- Biomarker of exposure (e.g., body burden)
- Biomarker of effect

Sources of Exposure Information

What are our sources of exposure information? The most commonly used in PGW studies to date is "self-report," that is, information from the subject about exposures. We would prefer independently documented information, such as industrial hygiene measurements or personal samplers, or even

biomarkers, either of exposure or effect. Usually, however, we have none of the above and must rely on modeling of exposure or dose.

Exposure modeling has important advantages. Extensive environmental or personal measurement programs are not needed; models provide estimates of population exposures using only a small number of measurements or plausible assumptions, and they can estimate exposures in situations where direct measures are not possible (e.g., unmeasured past exposures). But in using systems of equations to quantify or explain relationships between exposure and important variables such as emission rates or environmental parameters, they must make many assumptions and approximations. These assumptions or approximations may at times oversimplify the situation and distort the estimates. Albert Einstein once cautioned, "We must make our explanations as simple as possible, but not simpler." This is a wise thought to keep in mind about mathematical models, especially those that have not been validated against real data that is independent of the data which generated the model.

Modeling can be used in all phases of transport of the contaminant, from source to biological effect. Examples of source modeling include the use of emissions factors from oil well fires, or chemical fluxes through the water-air interface; of Fate and Transport modeling, Gaussian air dispersion models of oil fires or biodegradation of nerve gas agents in the environment; of receptor-activity modeling, the amount of water ingested daily in a desert environment by type of work; of toxicokinetic modeling, the elimination of chemicals and their metabolites as a function of time; and of Dose-Response modeling, various threshold or nonthreshold mathematical models that relate biological effect with amount of biologically effective dose.

In all discussions of exposure and dose, there remains the question of the correct "metric" to use: should the exposure be expressed as a "peak" value? a cumulative dose? a dose rate? If a particulate, what particle sizes are important? What about the particle's composition?

Exposure Misclassification

If exposure is not accurately determined, estimates of effect will be distorted. If the misclassification is made independently of the disease status of the subject (nondifferential misclassification), on average any true effect will be reduced, if there are two categories of exposure (e.g., exposed, nonexposed). But if there are three or more categories, the outer contrasts will be reduced, but any inner categories (e.g., a moderate category squeezed between a low and a high category) can move in either direction. One consequence of this is that an increasing dose-response relationship can easily be destroyed by a rather minor amount of nondifferential misclassification.

Differential misclassifications are also a serious problem. Measures of true effect can move in any direction, depending upon the exact mechanism of the misclassification. One common mechanism is unblinded assessment of exposure, which might assign a higher or lower exposure preferentially, given knowledge of the individual's disease status. When this happens in self-reported exposure information, it is called recall bias, or attribution. In either case it can cause spurious associations or raise the level of existing ones.

Imputation of Causality

Several "lists" or criteria of causality have been discussed in the epidemiological literature. It is important to note that none present requirements that *must* be met for a causal relationship to exist. They present only things that should be considered or evaluated. They include things such as the strength of the association, and whether a dose-response relationship exists. They are all subservient to the fundamental question, as expressed by A. Bradford Hill, one of the originators of the most famous of these lists:

"Clearly none of these nine viewpoints can bring indisputable evidence for or against a cause-and-effect hypothesis and equally none can be required as a sine qua non. What they can do, with greater or less strength, is to help us to answer the fundamental question--is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

Summary

Exposure assessment, while not everything, is extremely important, and should be practiced as part of good study design and intelligent interpretation. Poor exposure assessment can mask (even strong) associations, and can (easily) destroy existing D-R relationships. Significant obstacles exist to accurate exposure assessment in PGW studies: The similarity of the terrain and rapid troop movements make self-report more problematic; there were a large variety of potentially harmful exposures; there is sparse documentation of exposures. But epidemiology has learned a great deal in the past from imperfect exposure data, most notably in studies of diet and health. There is every reason to believe that the epidemiological method can also contribute to our understanding of unexplained illnesses among PGW veterans.

To do this will require clever methods to combine existing self-report, industrial hygiene and modeling data in ways that cross-validate and bound each other's uncertainties. Employment of validated exposure models and new biomarkers of exposure and early effect also hold promise.

Complex and Multi-exposure Responses

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The purpose for this presentation is two-fold: (1) to share some of the data from our past 15 years of research in toxicology of chemical mixtures; and (2) to suggest a realistic and workable approach for handling complex and multi-exposure toxicologic responses.

The importance of toxicologic interactions of chemical mixtures is underscored by a recent publication (Lazarou *et al., JAMA* 279:1200-1205, 1998) in which the authors reported that, in 1994, over 2.2 million hospitalized patients had serious adverse drug reactions (ADRs) and 106,000 had fatal ADRs. Thus, ADRs as a group is between the fourth and sixth leading cause of death in the U.S.

Regarding possible environmentally related exposures, the results from our past research endeavor included a 25-chemical mixture of groundwater contaminants from hazardous waste sites and a pesticide/fertilizer mixture. With the 25-chemical mixture, examples are presented for chemical-chemical interaction for immunosuppression in the form of reduction of bone marrow stem cell proliferation (Germolec *et al., Fund. Appl. Toxicol.* 13:377-387, 1989); chemical-biological agent interaction reflected by compromised immune-defense system in a host resistance assay (Germolec *et al., Fund. Appl. Toxicol.* 13:377-387, 1989); and chemical-physical agent interaction in which myelotoxic responses in mice were detected from the interactions of the 25-chemical mixture and radiation (Hong *et al., Toxicol. Lett.* 57:101-111, 1991). In addition, in vivo cytogenetic toxicity was seen in rats and mice exposed to a pesticide/ fertilizer mixture at ultra-low (ppb range) levels commonly detected in drinking water samples from certain areas in California with normal agricultural activities (Kligerman *et al., Mutation Res.* 300:125-134, 1993).

Toxicologic interactions go both directions; thus, antagonistic interactions are possible. We recently evaluated the combined carcinogenic potential of a mixture of four carcinogenic chemicals (arsenic, 1,2-dichloroethane, trichloroethylene, vinyl chloride) in the Multiple Organ Carcinogenesis Bioassay protocol advanced by Professor Ito and colleagues in Japan. Dose-related decreases of altered hepatic foci, bronchioalveolar hyperplasia and pulmonary adenoma were observed (Pott et al., unpublished results). In the case of pulmonary adenoma induced by the three initiators used, the four-carcinogen mixture actually reduced the tumor incidences to zero in all treatment groups.

To develop a method for handling complex chemical mixtures, a number of criteria must be met. These include: (1) utilize state-of-the-art science; (2) utilize computational technology; (3) advance interdisciplinary research beyond the normal boundary; (4) integrate biomedical research with mathematical/computer modeling; and (5) possess extrapolative and predictive capability. In our view, physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) modeling meets all the criteria described above. Several examples are presented on the application of PBPK/PD modeling of hepatotoxicity and carcinogenic processes of chemical mixtures. A conceptual model of neurotoxicity for Gulf War Veterans based on the publication of Haley and Kurt (*JAMA* 277:231-237, 1997) is also presented to illustrate the possible application of PBPK/PD modeling to Gulf War Syndrome.

In conclusion, based on our past research experience on the toxicology of chemical mixtures, the following points are emphasized: (1) Gulf War Illnesses, at least in theory, are possible with a sensitive population susceptible to chemical-chemical, chemical-biological, and/or chemical-physical agents under

extreme environmental conditions; (2) toxicologic interactions may be synergistic or antagonistic and some may be utilized to our advantage; (3) scientists conducting research in this area need to be unusually open-minded; and (4) integrated interdisciplinary research coupling math/computer modeling is a realistic and workable approach to deal with a complex problem such as Gulf War Syndrome.

Acknowledgment

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Measuring Reproductive Outcome

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This paper considers the methodological challenges facing researchers in the field of reproductive epidemiology. Particular methodological limitations and difficulties in studies of reproductive outcome related to Gulf War exposures will be addressed.

What Is Reproductive Outcome?

Successful reproduction begins with the production of functional gametes and ends with the birth of a healthy child who is able himself, or herself, to reproduce. Reproduction might thus be viewed as the cycling of the germ line from one generation to the other, and the child's health and subsequent reproductive fitness will be dependent on the exposure history of the maternal and paternal germ lines. The time period during which toxicity might occur begins with the conception of the child's parents and ends when the child reaches adulthood, a period that can be 30 or 40 years. This extended exposure period poses a particular challenge in epidemiological studies.

Many Endpoints, Some Very Rare

Adverse outcomes can occur at any stage in the reproductive process and can be considered as endpoints for epidemiological study (see Figure 1). These range from infertility in the male or female to cancer in offspring. Outcomes such as sperm abnormalities and early fetal loss are very difficult to measure in a nonclinical setting. Another issue is the rarity of certain outcomes, notably individual types of congenital malformation such Goldenhar syndrome, which has a prevalence of 1 in 3,000 to 5,000 live births.

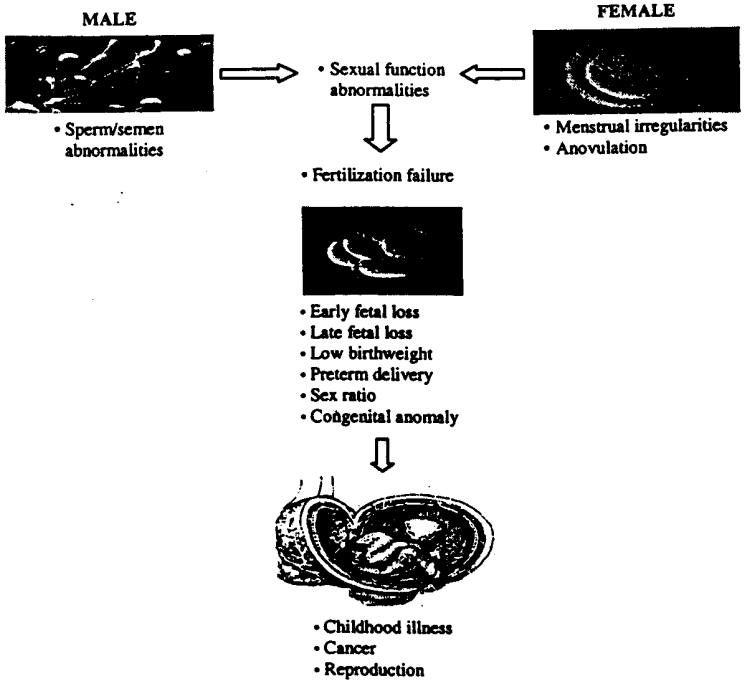

Figure 1. Endpoints in the Study of Reproductive Outcome

Male-mediated Developmental Toxicity

Until relatively recently, reproductive epidemiology was dominated by the study of female exposure to teratogens. Consideration of the male contribution to reproductive outcomes or endpoints is now a growing area of research. Male-mediated developmental toxicity, or MMDT, is be defined as the effect of exposures relating to the male parent that result in toxicity to the conceptus and abnormal development. Most of the evidence for such effects come from animal work, where the proposed mechanisms of action of an exposure are: induction of mutations during spermatogenesis, induction of cytogenetic anomalies, direct cytotoxic effects, concentration of toxic substances in ejaculate or sperm, disruption of imprinting, or epigenetic events. Although there is no unequivocal example of a link between human male exposure and a reproductive endpoint, there is increasing evidence of links among several types of chemical exposure and endpoints such as sperm quality, spontaneous abortion, congenital malformations and cancer in offspring. The chemicals in question include heavy metals, solvents, paints and pesticides. These exposures have particular relevance to studies of Gulf War veterans.

Design of Studies of Gulf War Veterans

Since the exposure in question, serving in the Gulf War, tends to be rare in the general population, most reproductive studies are of cohort, rather than case-control, design. The type of cohort study depends to a large extent upon the availability of recorded data. If accurate and complete records exist in the form of medical notes or registry information, recorded pregnancies can be linked to endpoints such as spontaneous abortion and congenital malformations. If there is poor recording or linkage, as is often the case for reproductive outcomes related to males, there may be no alternative but to obtain information from the study subjects themselves by survey. The advantage of the linkage approach is that the study can be performed, in theory at least, quickly and cheaply. A disadvantage is that the number of endpoints is limited by the availability of recorded data. The survey method is hampered by the logistic problems of tracking people and validating reported conditions. On the plus side, the survey method is able to investigate a variety of endpoints and thus obtain a more complete picture of reproductive health in the cohort.

Bias

Ideally, we would wish to study all the endpoints discussed above in all the people who served in the Gulf War (and all the people in the comparison group). In practice, we often deal with samples, usually have a limited number of endpoints for study, and always have lower than 100% response rates or linkage rates. Selection bias might operate if studies exclude certain members of the complete cohort, e.g., the separated veterans, and exclusion is related to the probability of adverse outcome. It is known that selection bias occurs in occupational cohort studies of reproductive outcome in women, but very little is known about such effects in men. Ascertainment of adverse outcome in linkage studies may also be biased if the outcome, e.g., congenital malformations, are not representative of all congenital malformations within the cohort. Biased response in surveys, whereby those with adverse outcomes are more likely to respond, is a recognized problem and poses a considerable challenge in the interpretation of "positive" findings.

Statistical Power

The rarity of certain endpoints has been mentioned. This poses a severe limitation on the ability to detect small effects, should they exist. As an example, in order to have 90% power detect a statistically significant ($P<0.05$) doubling of risk for an outcome with a expected prevalence of approximately 1 in 1,000, one would need to study over 10,000 children. The number of veterans required in the survey to obtain this number of children requires careful estimation. It is likely that many studies lack sufficient power to study endpoints rarer than 0.1%. This is particularly relevant when considering specific congenital malformations, making the interpretation of negative findings extremely difficult.

Conclusions

- Reproductive epidemiology covers a range of outcomes or endpoints that may span several generations.
- The interval between exposure and outcome can be long.
- MMDT in humans is plausible, but little unequivocal evidence exists to date.
- Studies of reproductive epidemiology, especially of male exposure, may suffer unique biases and confounding, which require careful consideration.
- Certain endpoints are rare, reducing the power to detect small effects.

The Biology of Stress

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Concepts of Stress

Concepts of stress have evolved over time and center on the idea that a living organism survives by maintaining a complex equilibrium, or homeostasis, that is constantly challenged or threatened by intrinsic or extrinsic disturbing forces or stressors. Hans Selye, the father of modern stress theory, stated it succinctly, "Stress is life and life is stress." Stress includes not only psychological or emotional events (as the term is popularly used), but also physical threat, trauma, surgery, metabolic derangement, serious illness, and infectious or noninfectious inflammation. Human beings also have the capacity to respond to anticipation of stress.

Stress response systems function to re-establish a steady state after a disturbance. Proper activity of stress response systems at rest and during superimposed stress are crucial for normal daily function and coping with stress. The two principal stress response systems are the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS). Both these systems are activated in response to stress, albeit to differing degrees, depending on the nature and intensity of the stimulus.

The recognition that the systems activated after stressors of widely differing natures led to the description of the general adaptation response. This response is characterized by central adaptation that leads to arousal, alertness, vigilance, enhanced cognition, focused attention, aggression, and inhibition of pathways that subserve vegetative functions. Peripherally, stress-adaptation is geared toward mobilizing energy for delivery to the central nervous system and critical musculature. Increased heart rate, blood pressure, and respiratory rate aid delivery of nutrients and oxygen. Gluconeogenesis and lipolysis increase production of energy. Growth and reproduction are suppressed, and suppression of the immune system leads to restraint of the inflammatory response. Due to the profound physiologic effects associated with activation of stress-response systems, they must be efficient in restraining their own activity by negative-feedback inhibition.

The HPA Axis

The HPA axis is generally considered to play a pivotal role in the coordinated physiological response to physical and emotional stress. Regulation of the HPA axis involves a complex array of biochemical events occurring principally among the hypothalamus, anterior pituitary, and cortex of the adrenal gland. Key among these biochemical signals are corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP), neurohormones with cell bodies in the medial parvocellular division of the paraventricular nucleus (PVN) of the hypothalamus. From there, neuronal projections transport CRH and AVP to the external layer of the median eminence. CRH is also widely distributed in other, extra-hypothalamic locations, including the limbic system, cerebral cortex, mid-brain areas, pons, and medulla. Acute stress results in the release of these peptides into the hypophyseal portal plexus. Stimulation of specific receptors for CRH and AVP on the corticotroph cells of the anterior pituitary results in the release of adrenocorticotropic hormone (ACTH) into the systemic circulation, primarily affecting glucocorticoid release from the adrenal cortex. CRH and AVP act synergistically, with AVP causing a tremendous amplification of CRH-induced release of ACTH. Indeed, evidence supports a role for AVP in sustaining the activation of the HPA axis during chronic stress.

Complex short and long negative feedback circuits, primarily mediated by specific glucocorticoid receptors (the so-called Type I and Type II receptors), converge to terminate activation of the HPA axis. Fast, or rate-sensitive, feedback is responsive to the rate of rise of circulating glucocorticoids and occurs within minutes of activation of the axis. Delayed, or genomic, feedback is mediated via specific types of

glucocorticoid receptors that inhibit transcription of critical genes such as those for the ACTH pro-peptide, and parvocellular CRH and AVP. The specific mechanisms underlying these and other modes of feedback inhibition remain ill-defined.

The particular supra-hypothalamic biochemical signals that affect activation of hypothalamic CRH and AVP in response to stress are equally complex, involving both peptide and catecholamine-containing neural pathways. Such pathways are usually redundant circuits, and are often composed of neuronal terminals which co-localize several peptide and non-peptide elements. Less well-studied than these biochemical signals, but of equal importance, are several specific neural circuits that have regulatory effects on the HPA axis. These areas include the amygdala, hippocampus, septal area, cingulate cortex, and certain brainstem regions.

In addition to its stress-dependent activation, the HPA axis exhibits a pronounced spontaneous near 24-hour, or circadian, rhythm. In humans, this circadian rhythm is entrained to the light-dark and sleep-wake cycles, with the trough of activity occurring in the evening and early night and the peak in activity occurring just before waking. Stress-induced secretion is superimposed on this basal circadian rhythm. There is evidence that the stress responsiveness and negative feedback regulation of the HPA axis varies across the day; hence, specific alterations in the timing, intensity, and duration of any stressor may result in widely varying patterns of HPA axis perturbation. It is thought, however, that under normal conditions the HPA axis may be a "closed loop" system, such that activation of cortisol secretion by stress will result in a compensatory decrease in circadian drive for cortisol secretion with maintenance of 24-hour integrated cortisol levels in the "normal" range.

Modulation of the Stress Response

In reviewing stress-response systems, it is important to keep in mind that activity of stress-response systems are determined by genetic and environmental factors. By way of example of the importance of genetic factors, Sternberg, Wilder and colleagues demonstrated blunted HPA axis responses to a variety of stressors in Lewis rats, while Fischer rats demonstrate exaggerated HPA axis responses when compared with outbred rats. Lewis rats also show differences in levels of CRH and AVP peptide hormones, as well as receptors for serotonin, when compared with Fischer rats.

A series of experiments by Meaney and colleagues point out the importance of neonatal environmental influences in determining life-long HPA axis responses to stress in rats. Early life stresses lead to changes in the dynamic function of the HPA axis that are detectable throughout life. The postnatal stress paradigms used in these experiments include neonatal handling (removing pups from the mother and home cage for 15 minutes daily from days 2-14 of life), maternal separation (the same procedure for 180 minutes), or neonatal endotoxin administration on postnatal days 1 and 3 compared with undisturbed pups. HPA axis function at baseline and after stress is evaluated when the rats reach adulthood (3-4 months). They demonstrated that pups subjected to handling had a reduction in cortisol levels during and following stress, while rats subjected to neonatal maternal separation had an increase in cortisol response as compared to the control animals. Pups treated with a different type of stressor, low dose endotoxin, in the neonatal period, exhibited HPA axis alterations characterized by increased ACTH and cortisol response to stress as adults. Differences in cortisol responses in these paradigms were paralleled by differences in hypothalamic CRH mRNA. In addition, postnatal handling of rats is associated with increased density of glucocorticoid receptors in the hippocampus, while maternal separation and endotoxin treatment led to decreased hippocampal glucocorticoid receptor levels. These experiments demonstrate that changes in HPA axis function can be mediated by differences in levels of regulatory peptides or hormones, and changes in receptor levels or occupancy.

Exposure to stressors during adulthood also alters HPA axis hormone levels and function. Rats chronically exposed to cold demonstrate normal basal ACTH and corticosterone activity, but HPA responses to novel stimuli are greater than normal, and, after novel stressors, the sensitivity of ACTH secretion to glucocorticoid inhibition is reduced. In contrast to neonatal paradigms where changes in

AVP and CRH levels are parallel, in some postnatal stress paradigms, such as adjuvant arthritis and chronic cholestasis, CRH levels decrease while AVP levels increase.

A series of experiments by Sapolsky and colleagues after close observation of olive baboons (Papio anubis) in a national park of the Serengeti gives insight into societal and personality factors that may account for some of the individual variability observed in stress-response systems. Baboons are social primates with a well-defined hierarchical societal structure. The animals studied have few external stressors in their environment, so that the majority of stress is social or psychological and due to competitive interactions with other members of the society. In males, rank order is the predominant factor that determines activity of stress response systems. Dominant males have lower basal cortisol concentrations, a larger and faster stress-response, faster recovery, and greater sensitivity to negative feedback inhibition. They are more resistant to the suppressive effects of stress on testosterone concentrations. Dominant males have lower basal blood pressure, a faster and larger rise in blood pressure and heart rate in response to a stimulus, and a faster recovery. There are modifiers to the predominance of rank order. For example, males that demonstrate affiliative (nonsexual) relationships with females and have positive interactions with infants have lower cortisol levels than males of comparable rank that fail to exhibit these behaviors. Taken together, these data suggest mechanisms by which individual variations in stress-response systems may occur.

Summary

Stress response systems play an important role in basal physiology and the ability of an organism to return to homeostasis after exposure to stress. Variability of stress-response systems may be genetic, the result of experience, related to chronic stress, and modified by social interactions. Perturbed function of these systems is associated with a number of somatic and psychiatric disorders. Study of the function of stress response systems may lead to improved understanding of the physiologic basis for medical disorders associated with stress.

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Communicating Health Risk Information Lessons-Learned

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Perhaps the most striking characteristic of risk in the last decade is the extent of public concern that has been expressed in litigation, political re-dress and in extensive and dramatic media coverage.

Why is effective communication of health risk information so important?

- High level of public interest in the problem
- Public acceptance of a solution depends on participation and understanding
- Personal credibility of agencies, institutions, and individuals depends on the ability to communicate

Technical Approaches

To some extent, risks can be measured in terms of actual physical damage, illness and disease. But the nature and extent of most risks are intrinsically uncertain and therefore the focus of scientific dispute. Uncertainties occur at all levels: the methodology to approach the problem; the potential health effects; the level of public involvement; and the difficulty of explaining the uncertainties that exist because scientific information is not available. If the underlying premise is that communication of risk information is fundamentally a technical issue, we still need to improve our efforts. Appropriate activities should be considered early in the planning process and address the following questions:

- What does a research priority list mean?
- For what purpose was this field of research chosen?
- What are the specific chemicals, substances, compounds, and methodology that will be studied?
- How were these items selected for study?
- Who selected these items and how?
- How can additional items be added or subtracted for study?
- How and what will intended audiences be told during the research process?

Beyond the Technical Model

A number of approaches to risk communication still emphasize the "sender-receiver" or "transmission" focus of providing information. This one-way technical model, ascribing a passive reception role to the "receiver" is supportive of an active all knowing communicator who determines what risk messages are to be sent, the channel and the intended audience.

As the 21st century rapidly approaches, alternatives to the technical approach are promising. Responses of various population samples, opinion surveys and planning guides suggest consensus agreement that communication about risk to health should be an interactive process involving information exchange between sources and the intended audience.

Four factors continue to complicate public communication as follows:

- Lack of clear health statements reflect the uncertainties and limits of scientific understanding
- Major problems result from limitations in the credibility of those communicating risk information
- Channel problems reflect the limitations of computer and media-based health communication information
- Receiver problems result from the biases, beliefs and perception of recipients of information

Further complicating these problems is the fact that health risk communication is fundamentally a sensitive area because of its influence on public perceptions and behavior, the practices of health professionals, and in the impact on the legislative process.

Credibility

Lack of credibility negatively alters the communication process by adding distrust and acrimony. How then do we earn trust and credibility? The following are proposed as guidance:

- Involve the intended audience early
- Pay attention to the soundness of the process
- Work with locally recognized organizations, leaders and media
- Listen to the concerns and needs of the audience
- Provide information in an appropriate form to meet needs;
- Explain Agency or Institution procedures and limitations
- Make access to useful information easy and simple

Shaping the Reporting of Risk

For many groups in the United States, the visual and print media dominate the avenues of public information. They serve as filters through which people receive news and interpret information. Through their coverage or non-coverage of issues they set the agenda of public discourse and guide personal behavior. The media's primary strength has been aptly described as agenda setting and not necessarily in reporting "facts" as provided by scientists and health risk communicators. An important effect of media coverage is to establish a framework of expectations. Defining a framework or a text in which related events can be interpreted must be considered a critical role for health risk communication specialists. Developing such a framework can be guided by several important "lessons-learned" as follows:

- Research is not a big story
- Politics is often more newsworthy then science
- Risk is simplified to a dichotomy: is it safe or not?
- Risk information is often personalized
- Claims of risk are usually more interesting than claims of safety
- Reporters do their job with limited time and expertise and often need and want assistance

Electronic Communication

The electronic superhighway offers the technological possibility of reading a tailored newspaper each day dealing with specific health risks of concern. Except this newspaper would be electronic. Although these new opportunities for faster and technologically sophisticated information systems are exciting they do not alone improve our ability to better communicate hazard information. The problem with standalone technologically advanced transmission channels is that learning is seen as passive, with the learner simply taking in information. The history of health risk communication in the last decade supports the contention that there is no information in printed on electronic media or in any medium *per se*. If communications do "contain" something of value, this is only "word" rather than information. Information and meaning arise only in the process of listeners, readers or viewers actively making sense of what they hear or see, which is particularly critical in public health decision making.

In conclusion, what are the lessons-learned in health risk communication? Lessons-learned are summarized in the following seven cardinal rules plus one:

- Client focus
- Client focus
- Client focus
- Client focus
- Client focus
- Client focus
- Client focus
- Client focus

NOTE: Health Risk Communication Guidelines are now available

The Presidential Advisory Committee on Gulf War Veterans Illnesses recommended that the National Science and Technology Council (NSTC) develop an interagency plan to address health preparedness for readjustment of veterans and families after future conflict and peacekeeping missions. The report from the subsequent Presidential Review Directive (PRD)/NSTC-5 has now been published. The report entitled *A National Obligation: Planning for Health Preparedness for and Readjustment of the Military Veterans and Their Families after Future Development*, contains a 20-page detailed "Guide to Health Risk Communication" including recommended strategies and objectives (see Appendix A).

The report is available from the NSTC Executive Secretariat at (202) 456-6100 or by e-mail request to the author of this presentation at MRL1@CDC.GOV.

COMMUNICATING EXPOSURE ASSESSMENT AND CLINICAL OUTCOME RESULTS TO VETERANS EXPOSED TO DEPLETED URANIUM DURING THE GULF WAR

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The Depleted Uranium (DU) Program must communicate complex exposure assessment information and clinical outcome results to its participants who were exposed to depleted uranium (DU) during the Gulf War. This challenge is amplified by the circumstances of exposure, the lack of conclusive medical and scientific data on human exposure to DU and the presence of factors known to increase the magnitude of the perception of risk.

During the follow-up medical evaluation of the DU Program participants, focus groups were conducted to assess information needs, general levels and areas of concern and preferred methods of communication. The focus group findings revealed concerns related to individual medical issues, especially reproductive health concerns, group medical issues and issues of the surveillance process. A review of the focus group findings will be presented.

The focus group findings provided the basis for subsequent communication with the participants. A formative evaluation of the communication process was conducted after several mailings of exposure and clinical information. A survey evaluating comprehension, attitudes and changes in level of concern was included in a packet communicating whole body radiation counting results.

Twenty-six (26) DU exposed participants and nineteen (19) unexposed controls who underwent whole body radiation counting and received the packet of results completed a self administered survey. Twenty (20) DU exposed participants and fifteen unexposed controls completed the survey.

A comparison of cases and controls with respect to comprehension of their results, preferred methods of communication and levels of trust will be presented. A comparison of beliefs about the accuracy of the information and the levels of concern and anxiety between the highly DU exposed and low DY exposed groups will also be discussed.

KEYWORDS: RISK COMMUNICATION, DEPLETED URANIUM, VETERANS

Treating Difficult to Diagnose and Ill-Defined Conditions: Translating New Advances in Our Understanding of Mechanisms into More Effective Treatments

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Background

Most of the research on GWI has focused on the "unexplained" symptoms and conditions that have affected tens of thousands of veterans who were deployed to the Persian Gulf during Operations Desert Shield and Desert Storm. These illnesses are "unexplained" because those afflicted generally suffer from one or several nonspecific symptoms such as fatigue, memory problems, and/or pain in various areas of the body, but we are not certain of the precise physiologic cause, nor of the treatment.

Although much remains unknown about these conditions, there are several facts that have emerged. The first is that there is no single unique or discrete illness that occurs in persons who were deployed to the Persian Gulf. Instead, these individuals appear to suffer from the same patterns of symptoms that afflict tens of millions of Americans, and go by terms such as FM, CFS, MCS, and so forth. Also, in some cases, both GW veterans and individuals in the general population with these symptom complexes are inappropriately labeled as having a psychological problem. The lack of a single definition for these illnesses, or of any laboratory or diagnostic tests that can establish the diagnosis, causes considerable problems in treating and researching these conditions.

The second important point about these types of illnesses is that many different types of environmental exposures can apparently trigger the same symptom complex. Most persons are well aware of the debate that has transpired with respect to the cause(s) of GWI. There appears to be a wide chasm between two seemingly disparate views: those who feel that these illnesses were triggered by "stress," and others who feel that toxins or infectious agents were involved. The scientific reality is that toxins and infectious agents can act as biological "stressors," just as physical trauma, drugs, and emotional stress do. Just as there are many different types of "stressors" that appear to be capable of triggering or worsening FM, CFS, and MCS, there are likely to be a plethora of exposures that might have contributed to the development of GWI.

With this in mind, our current state of knowledge regarding several important aspects of illnesses such as FM, CFS, and MCS will be reviewed, and in each section, the implications of these findings on treatment will be emphasized.

I. Epidemiological Considerations

FM, as defined by 1990 American College of Rheumatology (ACR) criteria (chronic widespread pain and 11/18 positive tender points), is very common, affecting 2% - 4% of the population in industrialized countries. Chronic widespread pain is even more common, affecting approximately 10% of the population, and chronic regional pain affects 20% - 25% of the population. In many of these persons with chronic pain there is no damage or inflammation in the painful region that can adequately explain the physiologic basis of the pain.

CFS is slightly less common than FM, and is defined on the basis of severe fatigue, as well as the presence of four of eight "minor" symptoms, including myalgias, arthralgias, sore throat, tender nodes, headaches, cognitive problems, postexertional malaise, and sleep difficulties. Again, although chronic fatigue "syndrome" only affects about 1% of the population, the complaint of chronic fatigue is very common, affecting 10% - 20% of the population.

There is no widely accepted definition for MCS, but a generic definition is that individuals will experience symptoms in several organ systems in response to being exposed to several multiple types of environmental stimuli.

There are several important findings that have been brought to light by epidemiological studies of these disorders. The most important is that all of the defining features of these conditions occur as a continuum in the population. Thus, pain, tenderness, fatigue, and "chemical sensitivity" all are distributed over a wide range in the population. For example, there is not a small group of persons who are "tender" and another large group who is "nontender." Instead, there is a wide range of tenderness in the population. The same holds true for pain, fatigue, chemical sensitivity, etc. This does not minimize the impact of these symptoms in a given individual when the symptoms are qualitatively more severe or more frequent, but instead points out how difficult it is to define these illnesses.

The second important point is that somatic symptoms such as chronic pain, fatigue, memory problems, etc., aggregate in the population. This is one reason that there is considerable overlap between systemic conditions, e.g., FM, CFS, MCS, and GWI, as well as "organ-specific" diagnoses, e.g., Irritable Bowel Syndrome, and migraine and tension headaches.

Summary

The criteria for illnesses such as FM and CFS are artificial and arbitrary, and they do not define unique or discrete diseases. Many people meet ACR criteria for FM or Centers for Disease Control and Prevention (CDC) criteria for CFS, but far more have some element of these illnesses. Epidemiological studies of the prevalence and distribution of pain, fatigue, tenderness and other related symptoms in the population suggest that all of these symptoms occur as a continuum and co-aggregate.

Implications for treatment

The mechanisms operative in CFS and FM are likely to play a role in many persons who do not "meet criteria" for these illnesses. These persons with "a little FM" may respond well to the treatments we typically reserve for FM.

II. Psychobehavioral Aspects of Chronic Pain and Fatigue Syndromes

The rate of psychiatric co-morbidities in persons with FM or CFS appears to be partially dependent on the population under study. As high as 40% - 50% of persons with FM or Irritable Bowel Syndrome may have an identifiable psychiatric co-morbidity in tertiary care settings, but the rate may approach that of the general population in a population-based sampling.

Although the emphasis in these illnesses had previously been placed on concurrent psychiatric conditions, many now feel that these are not as important as other psychosocial factors. For example, it is being increasingly recognized that identifying and treating "maladaptive illness behaviors" may be much more important in these illnesses than psychiatric diagnoses. Maladaptive illness behaviors are patterns of behavior or cognition that worsen their symptoms or interfere with a person's recovery or improvement from a chronic illness. An example is that patients with these types of conditions will have "good" and "bad" days, and not infrequently will develop a pattern of attempting to do too much on a "good" day, which leads to several "bad" days. Since these are behavioral rather than biological processes, they are unresponsive to pharmacological manipulation. Cognitive behavioral therapy (CBT) identifies and addresses maladaptive illness behaviors and teaches techniques that focus on improving symptoms. CBT has been shown to be efficacious in nearly all of the disorders in this spectrum, including CFS and FM, as well as in other chronic medical illnesses such as cancer, rheumatoid arthritis, and post-MI patients. The best such programs are "medicalized," self-limited, and address primarily cognitive processes and maladaptive illness behaviors and not psychiatric issues.

Summary

The new model of these illnesses places less focus on identifying and treating concurrent psychiatric disorders (although this remains important), and more focus on techniques such as CBT.

Implications for treatment

Find or develop a good CBT program in your area. This is a relatively inexpensive intervention that is independently efficacious, and might act synergistically with other treatment modalities to increase the efficacy of adjunct therapies.

III. Potential Pathophysiologic Mechanisms - Pain Processing

Patients with FM and other illnesses within this spectrum have a generalized disturbance in pain processing. This is in contrast to the idea conveyed by examining for "tender point," which leads to the notion that tenderness is somehow restricted to only certain regions or tissues. In these conditions, all peripheral tissues and structures have a low pain threshold, with deep cutaneous structures (i.e., muscle) having the greatest increase in pain sensitivity. This decrease in pain sensitivity likely extends into visceral structures, which may explain the overlap with Irritable Bowel Syndrome, noncardiac chest pain, etc., where this has been demonstrated.

These widespread changes in pain processing are likely to be due to aberrant sensory processing in the spinal cord (e.g., dorsal column) or brainstem. They are supported by findings of high levels of pro-nociceptive substances (SP, NGF) in spinal fluid, and by abnormalities in pain processing structures on cerebral SPECT scanning.

This type of "central pain" or non-nociceptive pain is minimally responsive to drugs that act primarily in the periphery, e.g., NSAIDs, narcotics, and more responsive to tricyclic compounds, as well as other newer classes of drugs.

Summary

The "tender point" construct leads to the impression that the lowered pain threshold is restricted to certain regions of the body, when in reality the individual is more sensitive to pain throughout the entire body.

Implications for treatment

The tricyclic compounds (e.g., amitriptyline and cyclobenzaprine) appear to be the most effective drugs presently available for treating the pain component of FM. With aggressive strategies to increase tolerance of these medications (start low, increase slowly; doxepin elixir), most patients can get reasonable pain control, especially if augmented by analgesics and low-impact, aerobic exercise.

IV. Potential Pathophysiologic Mechanisms - Neuroendocrine and Autonomic Abnormalities

There are significant data supporting a global blunting of the human "stress response," including both the HPA axes and the SNS. In both of these systems there may be low baseline tone and an attenuated response to stressors. These changes are the opposite of those seen in major depression and different than that noted in other types of psychiatric conditions, e.g., PTSD. In contrast to the changes in pain processing, which are seen in most patients, these changes are seen in (sizable) minority.

There are increasing data that some of the laboratory studies suggesting immune (e.g., changes in NK number, T4/T8 ratios, mitogen stimulation) and "infectious" (global increases in antibody titers) abnormalities may be secondary to these neurohumoral effects.

Summary

A subset of patients with these disorders appears to have clinically significant autonomic and/or neuroendocrine dysfunction.

Implications for treatment

Although there are no supporting data, it appears that these problems improve with globally effective treatments (e.g., tricyclics, aerobic exercise, CBT). Drugs that act centrally to augment adrenergic tone (e.g., venlafaxine, bupropion) may act similarly, and one of the benefits of aerobic exercise may be to impact these biological functions. In some persons these problems can remain clinically significant and respond to specific testing (e.g., tilt table testing, TRH stimulation) and/or interventions (salt, mineralocorticoids, beta-blockers, growth hormone).

V. Potential Pathophysiologic Abnormalities - Disrupted Sleep

The precise relationship between poor sleep and these disorders has not yet been established. Studies have generally showed a poor relationship between the presence of any type of sleep abnormality and the presence of symptoms, although sleep is disturbed in groups of patients with FM and CFS. Also, some groups of patients with extremely fragmented sleep (e.g., sleep apnea) have a low rate of FM, challenging the notion that this is causal. Disturbed sleep, like neurohormonal changes, likely plays a significant role in causing some of the aberrant laboratory findings that have been noted in FM (e.g., low IGF-1).

Summary

At this time it is probably more accurate to view poor sleep as a symptom of these conditions, or a negative modulating factor, rather than a cause.

Implications for treatment

Some medications that can effect a global improvement in FM (e.g., tricyclics) can also improve sleep. Other medications (e.g., trazadone and zolpidem) may selectively improve sleep with seemingly little improvement in pain or other symptoms.

VI. Summary of Chronic Widespread and Regional Pain Syndromes

The chronic pain and fatigue syndromes represent a clinically and biologically overlapping spectrum of illnesses that affect a significant percentage of the population. There are data supporting the notion that there is a genetic predisposition to develop this spectrum of illness, and that a number of different types of "stressors" (e.g., immune, drugs, physical, emotional) can either initiate or exacerbate these conditions. Once this illness develops, individuals display dysfunction of various components of the central nervous system, which may largely explain the decreased arousal and fatigue, increased pain perception, and dysautonomia that variably characterize these entities. In some persons with these illnesses, psychological and behavioral factors play a significant role in symptom expression, and in inhibiting effective treatment.

There are several principles that are important in treating persons with these conditions. The first and arguably most important is to acknowledge that these individuals are ill, even if the precise physiologic basis for the illness is unclear. It appears to be important to get individuals to focus on wellness rather than illness, and "forward" (i.e., on what they need to do to improve) rather than "backward" (i.e., on who or what may have caused their illness). Patients also need to understand that these illnesses cause dysfunction rather than damage, and that symptoms can generally be controlled with therapy.

The best-established treatments for these conditions are low doses of tricyclic drugs, low-impact aerobic exercise, and CBT. With respect to both medications and exercise, beginning at very low levels, and increasing slowly increase compliance and tolerance. For patients who fail to respond to first-line therapy, other medications may be effective, including serotonin-reuptake inhibitors, and central adrenergic agonists.

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Force Health Protection

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Force Health Protection is a strategy to provide maximum protection to service members throughout their military service. The desired outcome is a healthy and fit force, fully protected from medical hazards throughout the military operational continuum.

As our Armed Forces adapt to global changes, our medical force must also adapt. This requires effectively and efficiently providing health services to forces engaged in supporting U.S. national objectives. Changes in our national and international security environment, advances in technology and the reengineering of our military force require reconsideration of our strategy, including the role of the military medical system throughout the full spectrum of conflict.

The Chairman, Joint Chiefs of Staff established Joint Vision 2010 as a common direction for the Services, commands and defense agencies as they prepare to meet future challenges. JV 2010 establishes a blueprint to leverage technological opportunities, ensures information superiority, and channels human vitality and innovation to achieve new levels of effectiveness in joint warfighting. These initiatives accommodate the new operational concept of Full Spectrum Dominance via the four tenets of dominant maneuver, precision engagement, full dimensional protection and focused logistics. These tenets form the conceptual template for our future.

Force Health Protection (FHP) is a tenet of Focused Logistics. The military medical community must adopt and accommodate this philosophy, translating it into getting the right medical asset(s) deployed to the right place at the right time.

Force Health Protection is a natural extension of JV 2010. As such, it is an intellectual foundation for the military medical community. Force Health Protection represents a dynamic continuum of care that:

- Combines continuity and change;
- Builds on Service strength;
- Focuses on the high quality of people;
- Integrates new and emerging technologies with operational health service support concepts;
- Enables dominant maneuver, precision engagement, full-dimensional protection, and focused logistics; and
- Challenges the FHP to create and develop innovative operational and organizational strategies to support our forces.

The FHP concept is founded on a healthy and fit force, casualty prevention and casualty care and management. The focus is on essential care in theater supported by lighter, mobile, tailorable medical capability, and rapid evacuation out of theater for definitive care.

This concept requires maximizing the synergistic effects of the Services medical elements through jointly coordinated, comprehensively planned and mutually supportive medical operations. The JHSS pillars are aligned and support the National Military Strategy.

The relationship is clear — Peacetime Engagement with a Healthy and Fit Force, Deterrence and Conflict Prevention with Casualty Prevention, and Fight to Win with Care and Management of Casualties. The foundation of the deployable JHSS forces is the CONUS based Military Health System (MHS) which emphasizes readiness, health promotion and managed care.

Healthy and Fit Force

A healthy and fit force is mission-ready and reliable in body, mind, and spirit. Achieving a healthy and fit force that is deployable upon demand requires a foundation of physical, mental, emotional, spiritual, and community wellness across the continuum of military health services. Force Health Protection requires that the forces supporting our national policies constantly be at a maximum achievable state of wellness and that health service programs and benefits be geared toward that end.

A healthy and fit force is defined by three core tenets: Body, Mind, and Supportive Environment. The core tenet of Body encompasses aspects of physical fitness, injury prevention, disease prevention, nutrition, and dental health. The core tenet of Mind contains integrated aspects of cognitive, behavioral, emotional, and spiritual health. The core tenet of Supportive Environment includes aspects of community and family, as well as occupational and environmental health.

Casualty Prevention

The enemy threat produces combat casualties and the health threat produces disease and non-battle injuries (DNBI). The enemy threat depends largely on the enemy's intent to inflict casualties. The health threat depends on a complex set of environmental and operational factors that combine to produce DNBI.

It is imperative to pursue force protection technologies — personal and collective protection, research in human physiology and endemic threat diseases, and to execute a comprehensive military medical surveillance strategy to prevent casualties.

Casualty Care & Management

The third component calls for deploying smaller, mobile, and capable units to provide essential care in theater. This requires well coordinated and integrated joint use of deployed medical resources. The major components are:

First response: Fosters the development of treatment practices and training, not only for medical personnel, but for any individuals available in the vicinity of wounding or injury, including the casualty.

Forward resuscitative surgery: Focuses on specific life-saving practices and core competencies to manage severe bleeding, airway compromise and life-threatening chest injuries, and to prepare casualties for evacuation.

Theater hospitalization: Provides the range of services and diagnostics commensurate with ensuring quality "essential" care and patients are able to endure evacuation to further definitive care facilities.

Enroute Care: Ensures patients are successfully transported from point of injury to definitive care by any mode of transport without clinical degradation.

Definitive Care: Establishes the capability to provide the full scope of services and care throughout the Military Health System to casualties evacuated from a theater of operations.

We must reconfigure the FHP continuum to support essential care in theater and rapid evacuation for definitive care. Our emphasis is to promote a healthy and fit force, casualty prevention, and care and management of casualties with highly capable HSS units. Innovative and calculated leveraging of emerging technologies coupled with information superiority will make our operational medical forces more capable in meeting future requirements to be flexible, tailorable, deployable and relocatable. Re-shaping our strategy now will ensure America's sons and daughters receive optimum health services today and in the 21st century.

Improving the Health of Our Military, Veterans, and Their Families
A Strategic Plan for Research

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Introduction

The appearance of a wide variety of symptomatic illnesses among veterans of the Gulf War, and the difficulties in understanding the nature and causes of these illnesses, led President Clinton to establish the Presidential Advisory Committee on Gulf War Veterans' Illnesses on May 26, 1995. This Committee was chartered to conduct an independent, open, and comprehensive examination of health concerns of Gulf War veterans. The Committee issued its Final Report[1] on December 31, 1996. The Final Report documented the Committee's findings on the government's response to Gulf War veterans' illnesses through outreach, medical care, research, efforts to protect against and to assess exposure to chemical and biological weapons, and coordination activities pertinent to Gulf War veterans' illnesses.

The Committee made a number of recommendations in all of the areas cited above; however, one recommendation will likely have long-lasting consequences for the way the Federal Government plans, executes, and follows up on health issues related to future military deployments. The Committee recommended that the National Science and Technology Council (NSTC), through its member agencies, develop an interagency plan to more proactively address issues of health and readjustment of veterans and families before, during, and after future conflicts and peacekeeping missions. In response to the Committee's recommendation, President Clinton issued a Presidential Review Directive (PRD)/NSTC-5 that directed DoD, VA, and HHS to review current policies and programs related to deployment health. From that review, the agencies were to develop a comprehensive plan that may be implemented by the Federal Government to better safeguard those individuals who risk their lives to defend our Nation's interests.

Plan Development

To carry out the Presidential Review Directive, an NSTC Interagency Working Group (IWG) was established. Members of the IWG were drawn from DoD, VA, and HHS. The IWG oversaw the work of four Task Forces that focused on 1) deployment health, 2) record keeping, 3) research, and 4) health risk communications. A critical element in the IWG efforts was incorporation by each Task Force of lessons learned from the Gulf War and other recent deployments such as in Bosnia and Somalia. Each Task Force was specifically directed to pay special attention to issues associated with chemical and biological weapons as well as to the impact of emerging technologies and international cooperation.

Lessons Learned from the Gulf War

During the Gulf War, the U.S. military carried out an enormously successful campaign to protect the health of service members during deployment to Operations Desert Shield/Desert Storm. However, the government's response to the health problems and concerns of veterans after their return from the Gulf War was not as successful. VA and DoD did implement health and readjustment programs to address the expected postwar health problems of veterans. Both departments underestimated, and were thus unprepared, to cope adequately with the breadth and magnitude of the health problems reported by returning veterans. Despite the exceedingly low number of combat and noncombat casualties during deployment, the health problems of returning Gulf War veterans presented new and unexpected concerns that included:

- The possibility of injury due to chemical and biological warfare agents,
- Concerns over chronic diseases due to infectious and toxic exposures,
- Unexplained postdeployment symptoms,
- Concerns over illnesses with long latency periods following exposure,
- Concerns over illnesses that might affect family members, close contacts and children conceived postdeployment, and
- Higher rates of motor vehicle injury and death, and of other accidental injury, among war veterans.

The Federal Government's initial response was slow, unplanned, and uncoordinated. As a result, efforts did not fulfill the expectations of Gulf War veterans and their families.

The Research Task Force and Its Strategic Plan for Future Deployments

This paper focuses on the research component of the more complete strategic plan contained in the document *A National Obligation: Planning for Health Preparedness for and Readjustment of the Military, Veterans, and Their Families after Future Deployments*[2†]. There was close coordination among each of the Task Forces of the IWG that led to the larger, integrated plan, but it is valuable to briefly examine the overall approach of the Task Force toward a research effort aimed at improving military deployment health.

The primary goal of the Research Task Force was to identify research priorities and identify gaps in the current portfolio of federally funded research. Special attention was given to research needs associated with chemical and biological weapons because of their emerging importance as potentially inexpensive yet effects means of mass destruction.

Assessment of the State of Research at the Time of the Gulf War

Many of the major health concerns and uncertainties identified after the Gulf War are similar to those associated with other major foreign deployments. The response to these concerns could have been more effective had there been a better understanding of the potential biological and toxicological associations between exposure and response. Better knowledge of biologically based relationships between specific exposures and specific health outcomes enhances: (a) analysis of potential causes of illnesses; (b) research and development on effective prevention, intervention, and treatment strategies; and (c) development of an accurate and effective risk communication plan to inform troops about potential exposure risks. Furthermore, if epidemiological researchers had comprehensive population-based troop health assessments and exposure-monitoring data and data systems, they might have been more able to define potential associations between exposures and outcomes following the Gulf War.

Attention to the uncertainties of exposure-related health outcomes during deployment could have resulted in directed (or focused) research efforts, the results of which could have been applied before and during these deployments to mitigate against adverse health outcomes.

Furthermore, population-based health assessments of troops before and after deployments could have improved the ability to answer readily the deployment-related health concerns of veterans. Such knowledge could have also helped to plan for future deployments. Although design, development, and implementation of databases are not research per se, they play an important part in the research process because the quality of these activities can have a significant impact on the ability of epidemiological researchers to answer important questions about deployment health. Consequently, this strategic research plan also describes database requirements necessary to enable the pursuit of research.

† As of this writing this document has been reviewed by the President's Council of Advisors on Science and Technology, and has been approved by the NSTC. It has not, however, been publicly released.

Strategic Research Plan Overview

The Research Task Force identified the following research needs as essential to the foundation of this research plan:

- Epidemiological research capability and capacity to investigate exposure-outcome relationships
- Focused research on deployment-related risk factors
- Epidemiological research-driven data and data system requirements for health outcomes and exposures (anticipated or novel)

The Research Task Force established six overarching goals with supporting objectives and strategies:

1. The Federal Government should have the coordinated capability to apply epidemiological research to determine whether deployment-related exposures are associated with postdeployment health outcomes.
2. The Federal Government needs to maintain a balanced research program targeted at: a) improved prevention, intervention, and treatment strategies for priority health-risk factors and exposures; and b) improved biologically based dose-response models.
3. The Federal Government should have the capability to systematically collect population-based demographic and health data to enable longitudinal evaluation of the health of all service personnel (active duty, reservist, national guard) throughout their military careers and after leaving military service.
4. The Federal Government should develop the capability to collect and assess data associated with anticipated exposures during deployments.
5. The Federal Government should establish the capability to monitor deployments for the appearance of novel or unanticipated health risks and to quickly deploy assets to collect and assess data relevant to newly identified threats.
6. The Federal Government should foster a wide variety of collaborative research efforts spanning all sectors of society (private, academic,and government), and reaching outward to allied nations.

A subpart of Goal 2 identified five health "research priority areas":

1. Chemical, biological, and radiological warfare agents
2. Stressors of deployment and combat
3. Emerging health concerns (new exposure threats)
4. Infectious diseases
5. Occupational risk factors and noncombat traumatic injuries

The execution of a comprehensive plan such as this requires the cooperation and coordination of a number of federal agencies. This is a challenge, considering that the Federal Government's investment in health research spans multiple agencies and is the primary source of health research funding in the United States. Consequently, responsibility for execution of this plan needs to reside within the appropriate operational and research infrastructures in different agencies. Coordination, however, must be at an interagency level. Based on missions, capabilities, and capacities, the three primary agencies that will bear the responsibility of implementing this strategy are the DoD, VA, and HHS.

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Health Status of Gulf War Troops: Lessons Learned

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Almost 8 years after the United States sent 700,000 military men and women to the Persian Gulf we still have many unanswered basic questions about the health of these veterans. Despite extensive investigation, numerous scientific reviews, and millions of dollars in Federally funded research, we cannot tell many of these Americans what is wrong with them, what made them ill, and whether they will get better. Although much remains to be learned from our Gulf War experience, we have learned a few important lessons that can help in our search for these important answers.

A brief review of the U.S. force deployment and subsequent troop health status is an appropriate starting point. Shortly after their return, many of the 700,000 combat veterans reported a wide variety of illnesses. Health registries created by both the Department of Veterans Affairs (VA) and the Department of Defense (DoD) catalogued these illnesses in almost 100,000 veterans. While most illnesses were predictable and expected in this age military population, almost 25% reported symptoms or illnesses that were unexplained, though some attributed them to combat-related stress. See Figure 1.

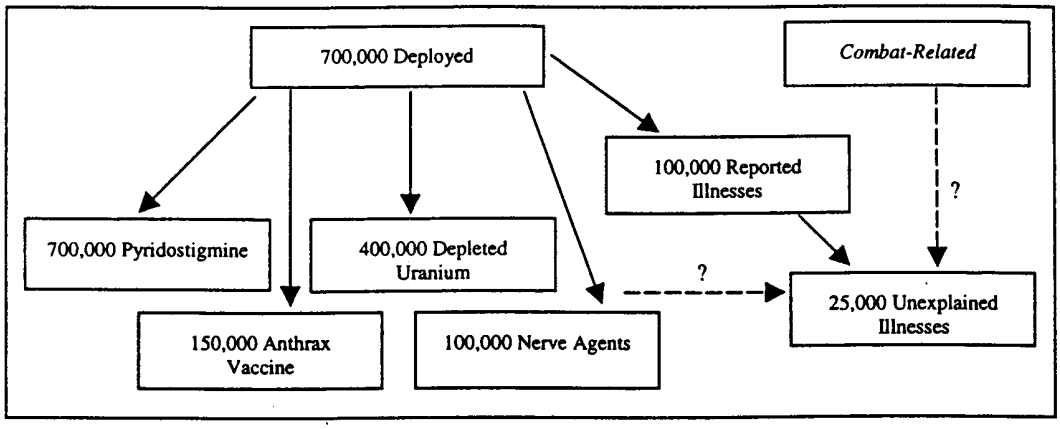

Figure 1. Health Status of U.S. Troops Who Served in the Gulf War

The inability to diagnose the nature of these ailments led to initial frustration, followed by anger and suspicions of some type of government cover-up. As more information became available detailing some of the potentially hazardous military occupational exposures associated with the Gulf War, veterans understandably assumed that these were the cause of their problems. Thus, potential exposures including pyridostigmine bromide, anthrax vaccine, depleted uranium, and nerve agent released by the destruction of captured Iraqi munitions were implicated in the unexplained illnesses. Concurrently, scientists and clinicians began to examine potential toxic materials that might cause illness several years later in exposed individuals. Unfortunately, the result has been too much focus on theoretical or alleged exposures to a variety of toxic substances, and too little focus on the sick veterans.

From this collective experience we have gained important information that should guide our continuing efforts to understand the health consequences of modern combat. We now know with a high degree of certainty that a single Gulf War syndrome cannot account for the many veterans with unexplained symptoms. Six expert scientific panels have each concluded that there is no unique Gulf War syndrome, but rather a variety of unexplained illnesses with overlapping symptoms. We have also observed that veterans of all major American military conflicts dating back to the U.S. Civil War have reported very similar unexplained physical ailments, thus providing compelling evidence that we are not dealing with a new, unprecedented phenomenon.

Lack of progress and frustration with the inability to identify a unique illness have caused many to shift their efforts toward speculation about causes of an undefined ailment. This, coupled with the inability to replicate combat situations and exposures in a controlled laboratory setting has slowed our quest for answers. Exposure risk research is not likely to provide answers for those veterans with ill-defined symptoms, but it may clarify some discrete illnesses and will provide valuable safeguards for troops who may be involved in future military deployments.

What is truly needed is a better understanding of symptoms and their relation to health and disease. We must also pursue a more thorough knowledge of the role of various stresses, including predeployment, combat, and postdeployment stresses in this relationship between symptoms and physical well-being. Additionally, we must compile replicable, case-control studies of ill Gulf War veterans, and careful long-term follow-up studies.

The complex interplay between myriad physical and psychological factors, coupled with the lack of predeployment baseline studies will make further progress arduous, but with diligence, patience, and rigorous adherence to good science we may be able to provide Gulf War veterans with some of the answers they deserve.